

Paracetamol

Dymadon®

Lemsip®

Panadol®

Panamax®

Tylenol®



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Indications

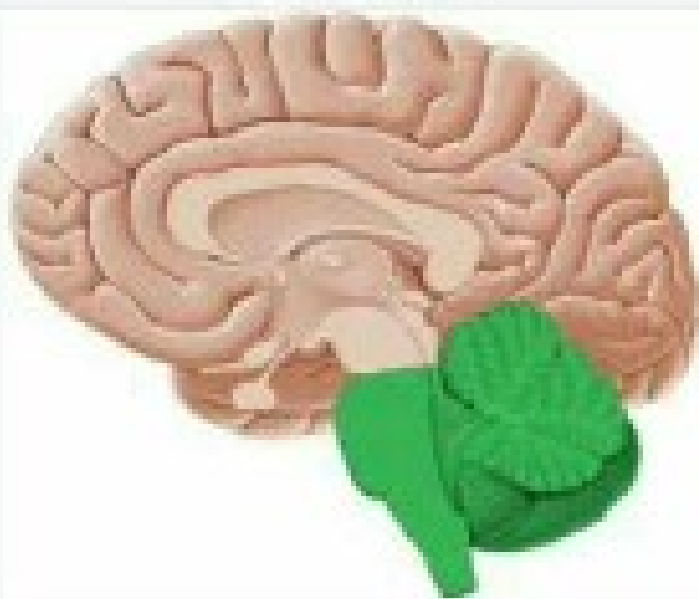
- ① Paracetamol is a **first-line analgesic** for most forms of acute and chronic pain.
- ② Paracetamol is an **antipyretic** that can reduce fever and its associated symptoms (e.g. shivering).



Mechanism of action

① Paracetamol is a weak **inhibitor of cyclooxygenase (COX)**, the enzyme involved in prostaglandin metabolism.

In the **Central Nervous System**



COX inhibition

- ① Increases the pain threshold
- ② Reduces PGE2 concentrations in the thermoregulatory region of the hypothalamus,
↓ fever.

Mechanism of action

② Paracetamol has **Specificity for COX-2** (The isoform induced in **Inflammation**) rather than COX-1 (The isoform involved in protecting the gastric mucosa and regulating renal blood flow and clotting).

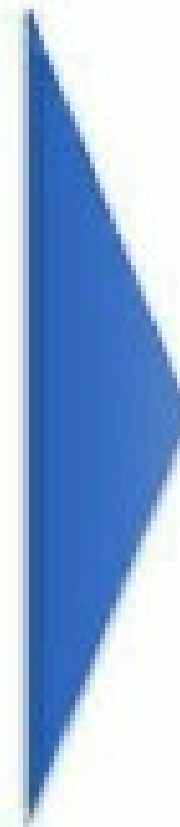
Note: Despite its **COX-2 selectivity**, Paracetamol is a weak anti-inflammatory, as its actions are inhibited in inflammatory lesions by the presence of peroxides.

Side effects

At treatment doses, paracetamol is very **safe** with few side effects.

Unlike NSAIDs

Lack of COX-1 inhibition means that it **does not** cause peptic ulceration or renal impairment or precipitate cardiovascular events .

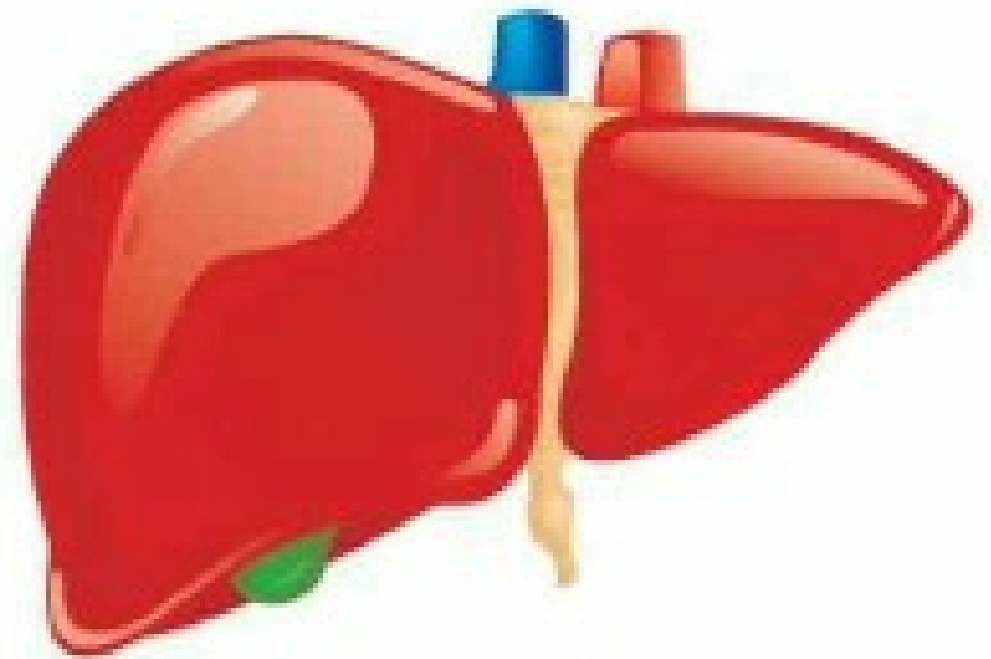


Its safety makes it a popular choice as a first-line analgesic.

Side effects

In overdose, paracetamol causes **liver failure**.

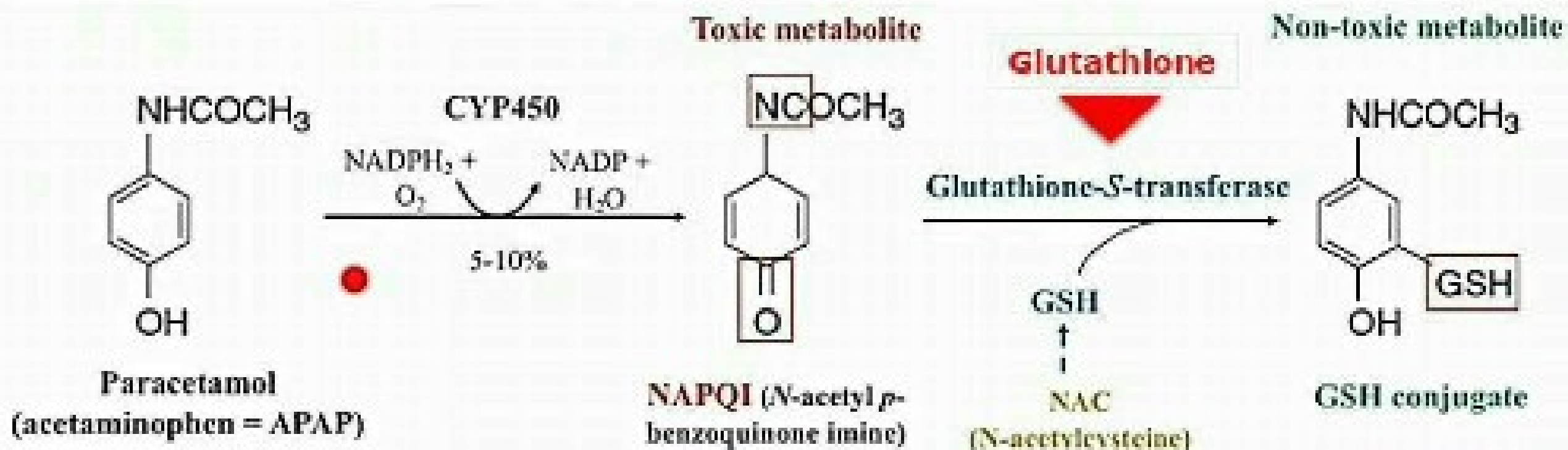
Paracetamol is metabolized by cytochrome P450 enzymes to a toxic metabolite, which is conjugated with glutathione before elimination. This causes depletion of glutathione in liver cells thus predisposes them to toxicity.



Hepatotoxicity can be prevented by treatment with the glutathione precursor **acetylcysteine**.

Side effects

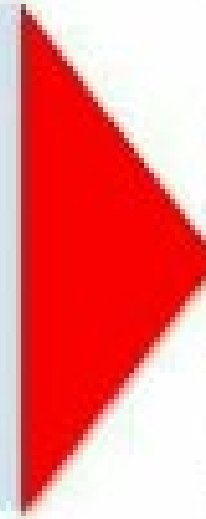
In overdose, paracetamol causes **liver failure**.



Warnings

Paracetamol dose should be reduced in people at increased risk of liver toxicity e.g.

- 1 Alcoholics**
- 2 Severe Malnutrition**
- 3 Severe hepatic impairment**



This is particularly important where paracetamol is given by IV infusion.

Drug interactions

There are **few clinically significant interactions** between paracetamol and other drugs.

Cytochrome P450 inducers, e.g. Phenytoin and Carbamazepine, increase the production of Paracetamol toxic metabolites (NAPQI) and thus risk of liver toxicity after paracetamol overdose.



How to prescribe it

Oral administration is the rule.

Note: *For patients unable to take drugs by mouth, paracetamol can be prescribed for IV infusion or Rectal administration.*

The usual adult dose is 0.5–1 g every 4–6 hours, maximum 4 g daily .



Administration

- **Oral** paracetamol is available as tablets, capsules, soluble tablets and oral suspension.



Intravenous paracetamol is pre-prepared as a solution that can be infused undiluted over 15 minutes or diluted in 0.9% sodium chloride or 5% glucose solution before administration.

Patient education

- Explain that you are prescribing paracetamol with the **aim** of reducing or relieving pain.
- Effects should be felt around **half an hour** after taking it.
- Where regular paracetamol is prescribed, explain the importance of taking it **every 6 hours**.
- **Warn them not to exceed the recommended maximum daily dose** because of the potential risk of liver poisoning.



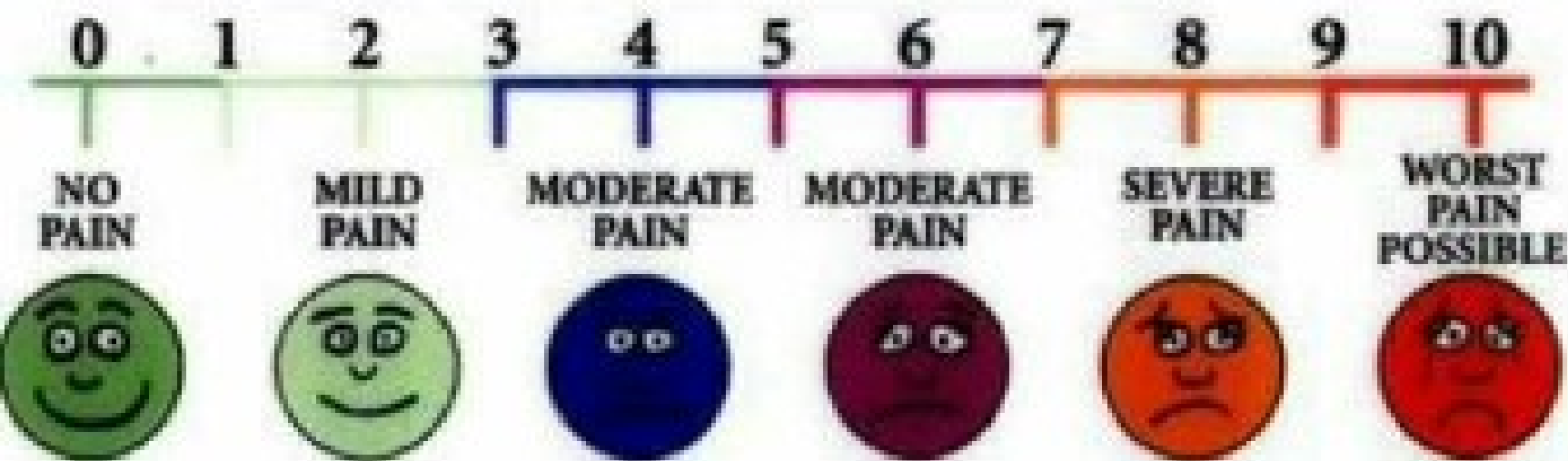
Patient education

Note: Many medicines purchased from the chemist (e.g. cold and flu preparations) contain **paracetamol**. The patient should check the label or ask the pharmacist before taking these with paracetamol.



Monitoring of the treatment

Efficacy of paracetamol in pain control can be established by **enquiry about symptoms** or by using a pain score, e.g. a visual analogue scale.



Monitoring of the treatment

After Overdose - **Blood Tests** Include:

- **Prothrombin Time (PT)** or international normalized ratio (INR)
- **Serum alanine aminotransferase (ALT)** activity
- **Creatinine concentration**

These measures are required to establish efficacy of acetylcysteine treatment and determine the need for further treatment.

INR is based on the ratio of the patient's prothrombin time and the normal mean prothrombin time

Monitoring of the treatment

After Overdose - **Blood Tests** Include:

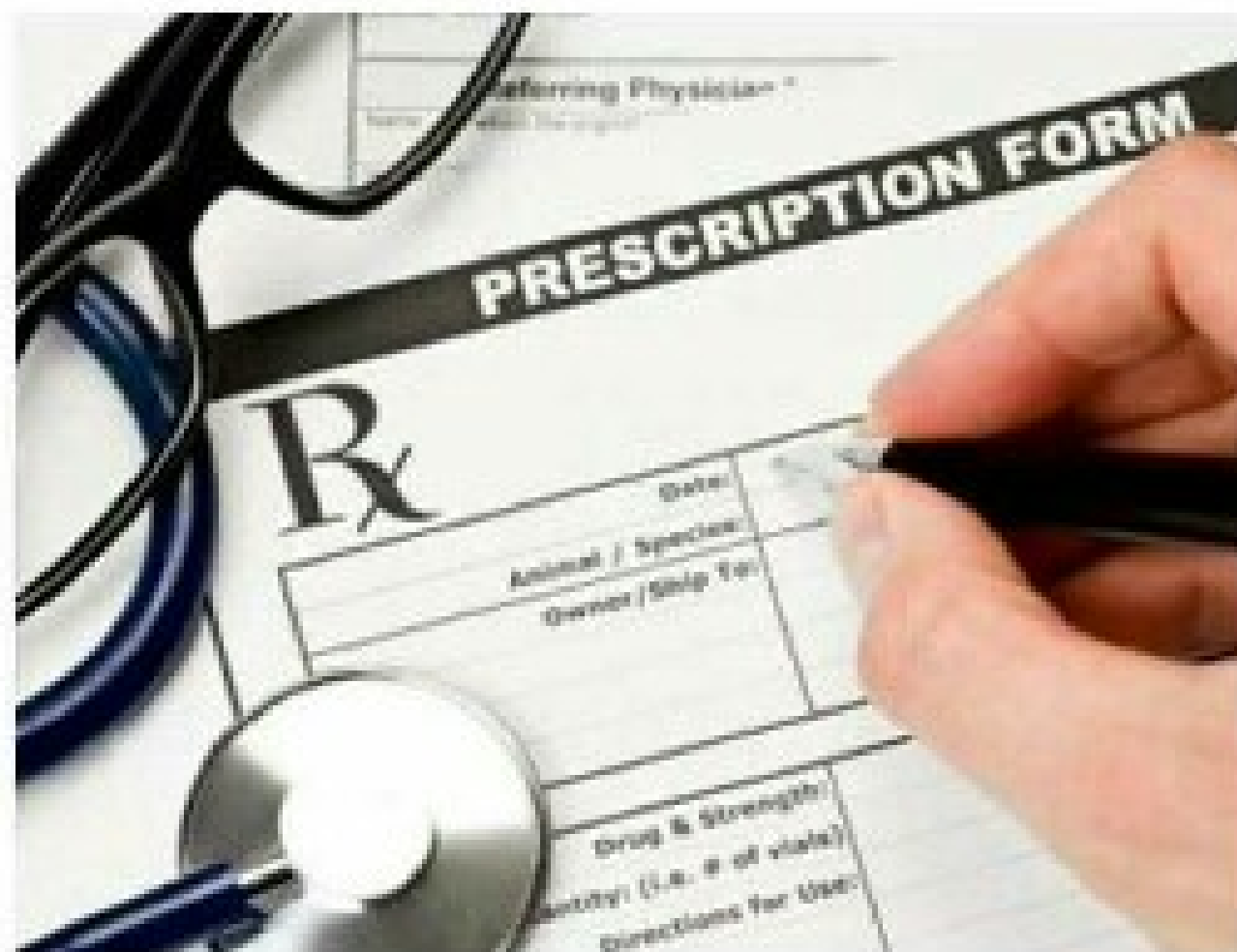
- **Prothrombin Time (PT)** or international normalized ratio (INR)
- **Serum alanine aminotransferase (ALT)** activity
- **Creatinine concentration**

These measures are required to establish efficacy of acetylcysteine treatment and determine the need for further treatment.

The most effective way to **diagnose poisoning** is by obtaining a blood **Paracetamol Level**.

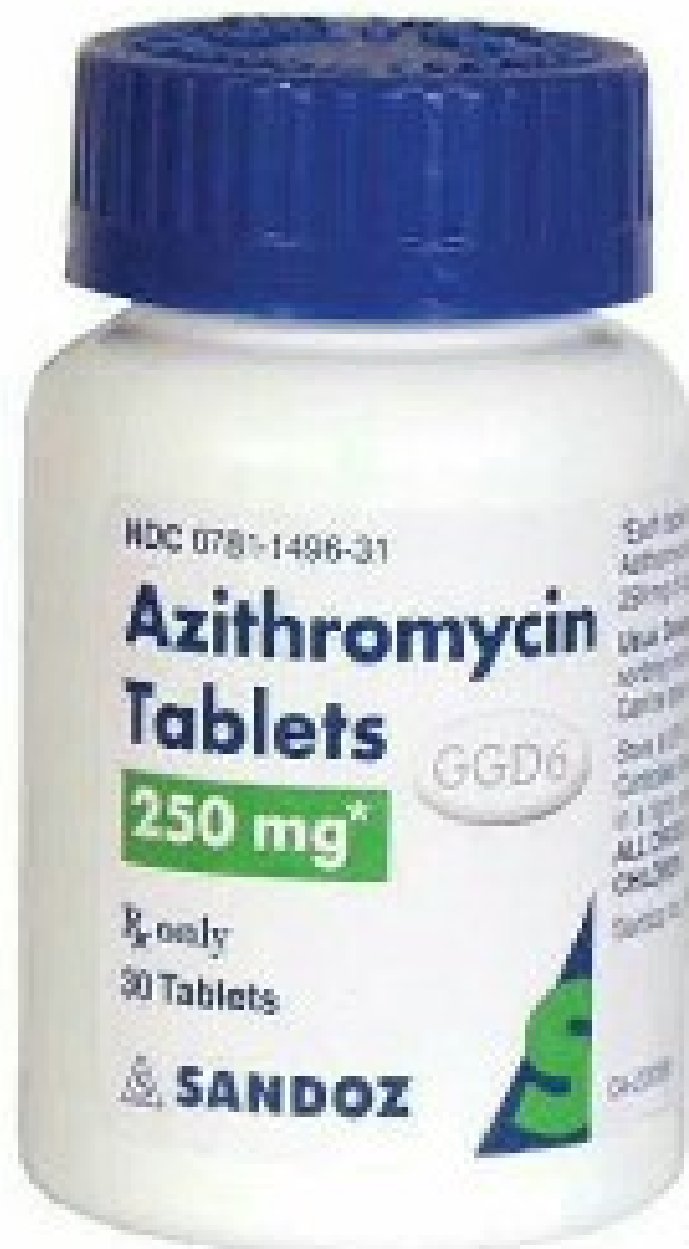
Clinical tip

- ✓ **Always** check that it has not already been prescribed.
- ✓ **Look out for 'co-' drugs** with 'hidden' paracetamol.



Macrolides

Clarithromycin
Erythromycin
Azithromycin



Rx
Required



Indications

- ➊ Treatment of **respiratory and skin and soft tissue infections** as an **alternative to a penicillin** when this is contraindicated by allergy.
- ➋ In **severe pneumonia** added to a penicillin to **cover atypical organisms** including *Legionella pneumophila* and *Mycoplasma pneumoniae*.
- ➌ **Eradication of *Helicobacter pylori*** (for example causing peptic ulcer disease) in combination with a proton pump inhibitor and either amoxicillin or metronidazole.

Mechanism of action

- ➊ Macrolides inhibit bacterial protein synthesis.
- ➋ They bind to the 50S subunit of the bacterial ribosome and block translocation
- ➌ Bacteriostatic
- ➍ **Erythromycin**, the first macrolide, has a relatively broad spectrum of activity against Gram-positive and some Gram-negative organisms.
- ➎ Bacterial resistance to macrolides is common, mainly due to ribosomal mutations preventing macrolide binding.

Synthetic macrolides:
(**Clarithromycin** and **Azithromycin**) have amplified activity against Gram-ve bacteria, particularly *Haemophilus influenzae*.

Side effects

Adverse effects are most common and severe with **Erythromycin**, but can occur with any macrolide.

Macrolides are **Irritant**, causing nausea, vomiting, abdominal pain and diarrhoea when taken orally and thrombophlebitis when given IV.

Other important side effects:

Allergy

Antibiotic-associated colitis,

Cholestatic jaundice,

Long QT interval

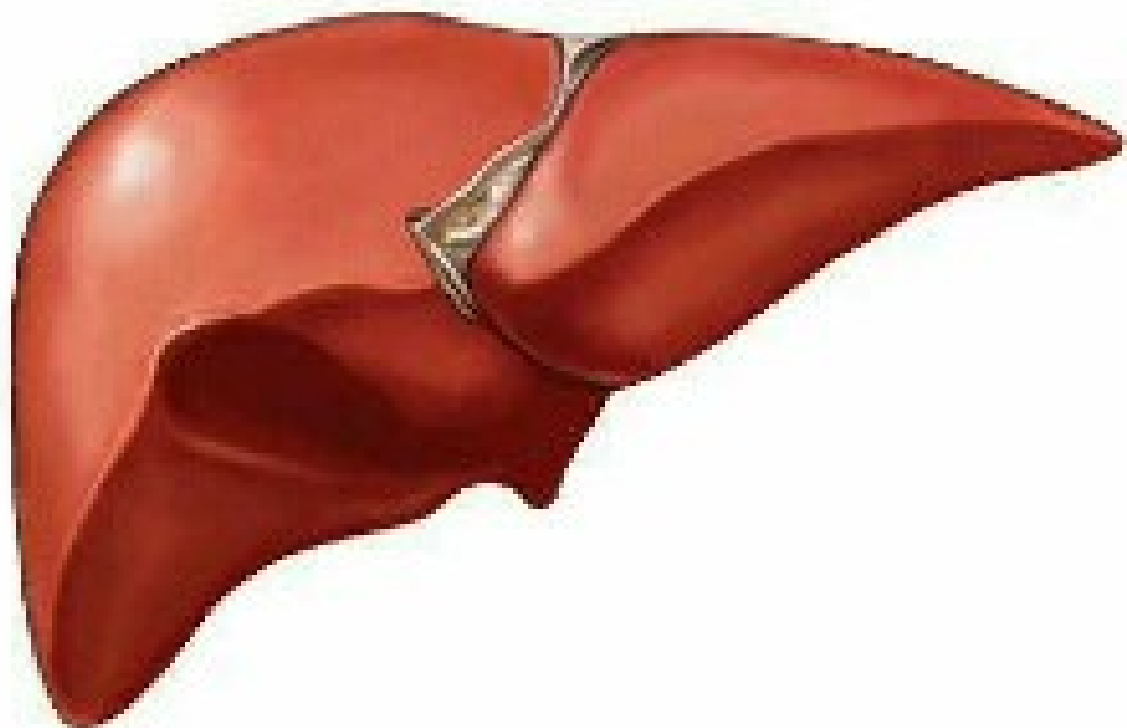
Ototoxicity at high doses.

Warnings

① Macrolides should not be prescribed if there is a history of macrolide **Hypersensitivity**, although they are a useful option where penicillin is contraindicated by allergy as there is **No cross-sensitivity** with Penicillin.

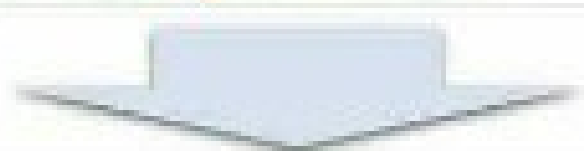
Warnings

② Macrolide elimination from the body is mostly hepatic with a small renal contribution, such that caution is required in severe **hepatic impairment** and dose reduction in severe renal impairment.



Drug interactions

Erythromycin and clarithromycin (**But not azithromycin**) **inhibit cytochrome P450 enzymes.**

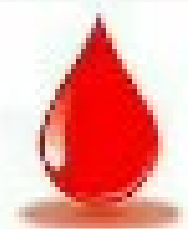


This increases plasma concentrations of drugs metabolized by P450 enzymes.

Warfarin



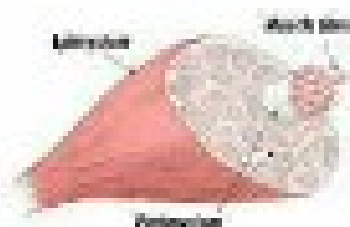
Bleeding



Statins



Myopathy



Drug interactions

Macrolides should be prescribed with caution in patients taking other drugs that **prolong the QT interval** or cause arrhythmias: e.g.



- 1 Amiodarone
- 2 Antipsychotics
- 3 Quinine
- 4 Quinolone antibiotics
- 5 SSRIs

How to prescribe it

Clarithromycin is the very commonly prescribed macrolide.

- ✓ **More stable** and causing fewer adverse effects than **erythromycin**
- ✓ **Cheaper** than **azithromycin** (which also is not formulated for IV administration).



How to prescribe it

- ✓ Clarithromycin is usually prescribed for **oral administration**, as it is absorbed readily in the intestine and has good bioavailability.
- ✓ It is prescribed **IV** where patients are unable to take or absorb drugs via the gastrointestinal tract (e.g. due to vomiting).
- ✓ The usual dosage is 250–500 mg twice daily for 7–14 days.

When writing an inpatient antibiotic prescription, always include treatment indication and duration to facilitate good antibiotic therapy.

Administration

- ➊ **Oral clarithromycin** can be taken as tablets or oral suspension with or without food (although food may improve gastrointestinal tolerability).
- ➋ **Intravenous clarithromycin** should be **diluted**, e.g. 500 mg in 250 mL sodium chloride 0.9%, then infused into a large proximal vein (to reduce the risk of thrombophlebitis) over at least 60 minutes (to reduce the risk of arrhythmias).
- ➌ It **Must not** be given as bolus IV or IM injection.

Patient education

① Explain that the aim of treatment is to get rid of infection and improve symptoms.



Patient education

③ Before prescribing, always check with your patient personally or get collateral history to ensure that they are not allergic to macrolides.



Patient education

④ Warn them to seek medical advice if a rash or other unexpected symptoms develop. If an allergy develops during treatment, give the patient written and verbal advice not to take this antibiotic in the future and make sure that the allergy is clearly documented in their medical records.



Patient education

② For oral treatment, encourage the patient to complete the prescribed course.



Monitoring of the treatment

Check that infection resolves by:

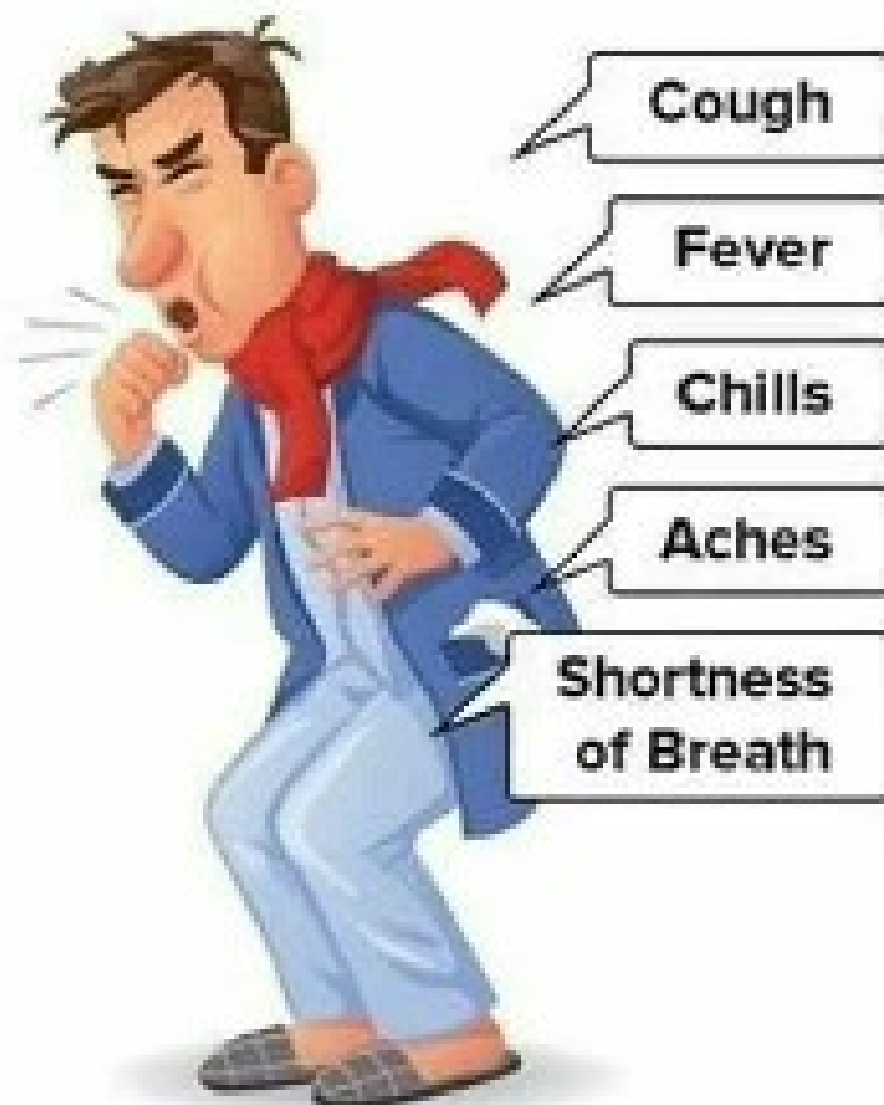
- ➊ **Patient Report** (e.g. Resolution of symptoms).
- ➋ **Examination** (e.g. Resolution of pyrexia, lung crackles).
- ➌ **Blood tests** (e.g. Falling C-reactive protein and white cell count).

Clinical tip



In patients with lower respiratory tract infections (LRTI), macrolides should generally only be added to penicillin treatment if there is evidence of pneumonia (e.g. consolidation on the chest X-ray).

Clinical tip



Macrolides are required to cover penicillin-resistant atypical organisms, e.g. *Legionella pneumophila* and *Mycoplasma pneumoniae*.

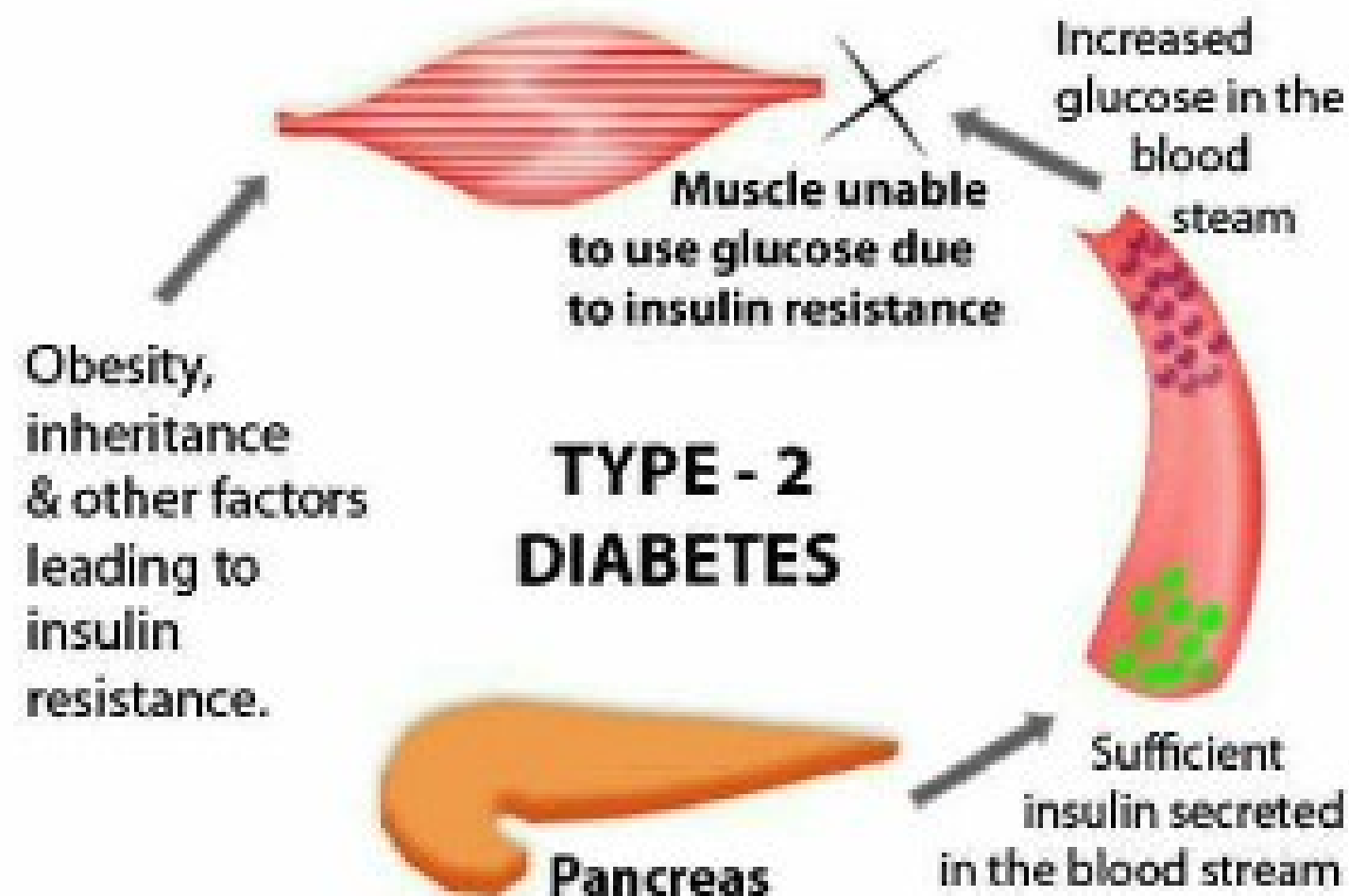
Metformin

Fortamet
Glucophage
Riomet
Dianben
Diabex



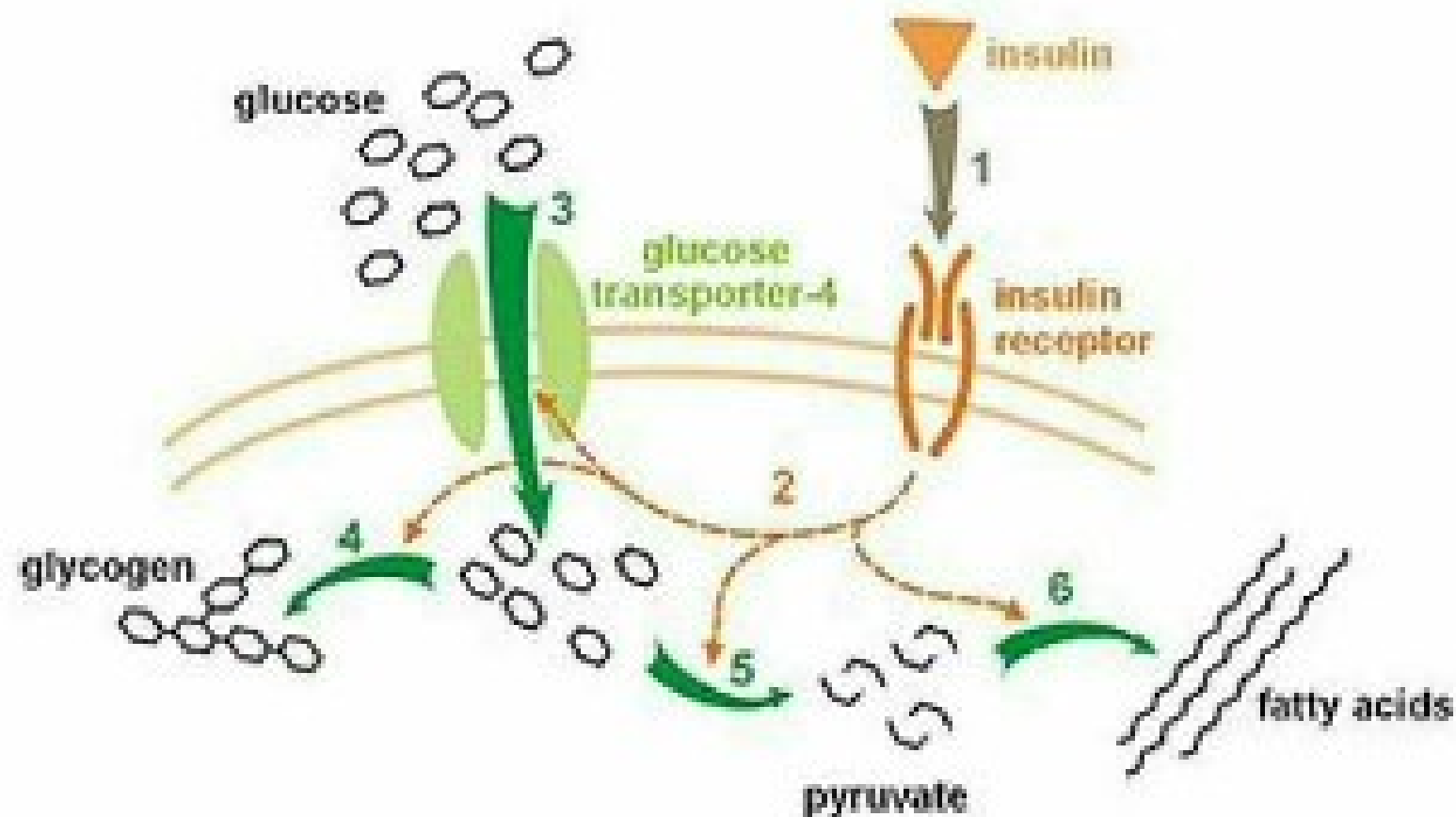
Indications

Type 2 diabetes mellitus, as **first choice medication** for control of blood glucose, used alone or in combination with other oral hypoglycemic drugs (e.g. sulphonylureas) or insulin.

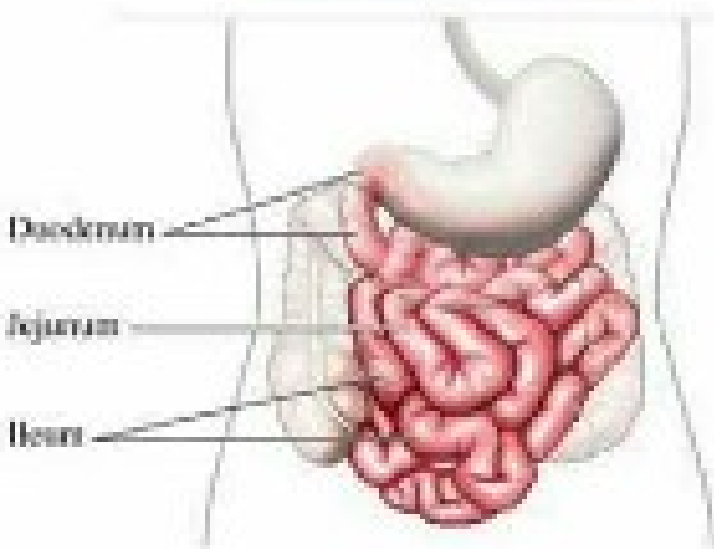
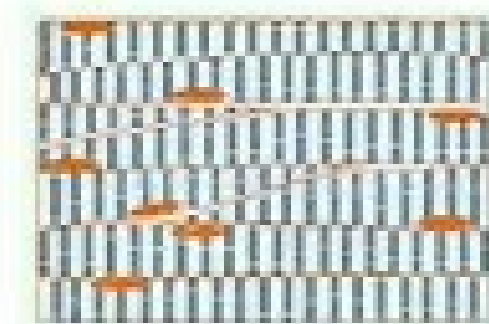
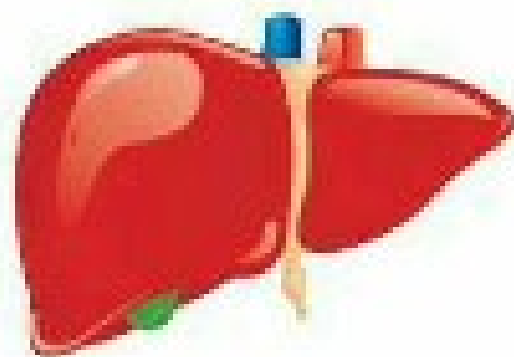


Mechanism of action

Metformin (a biguanide) lowers blood glucose by **increasing the response (sensitivity) to insulin.**



Mechanism of action

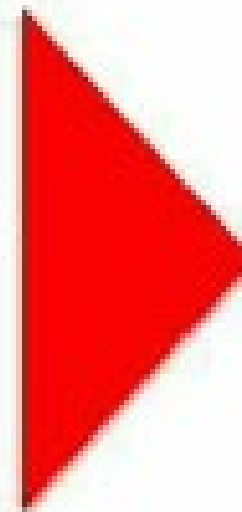


It **suppresses hepatic glucose production** (glycogenolysis and gluconeogenesis), increases glucose uptake and utilization by **skeletal muscle** and suppresses **intestinal glucose absorption**.

It achieves this by diverse intracellular mechanisms, which are incompletely understood.

Mechanism of action

It does not stimulate pancreatic insulin secretion and therefore **does not cause hypoglycemia.**



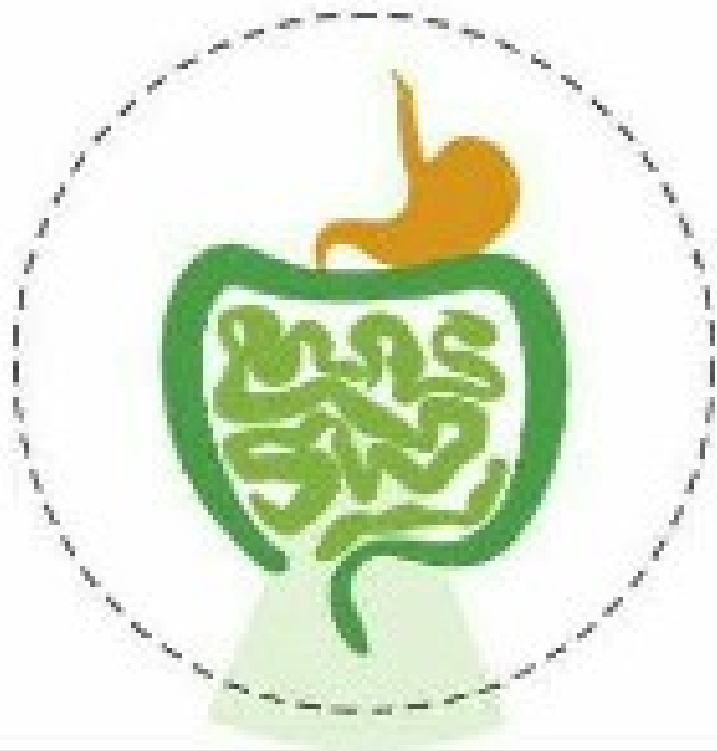
Mechanism of action

It **reduces weight gain** and can induce weight loss, which can prevent worsening of insulin resistance and slow deterioration of diabetes mellitus.



Side effects

① Metformin commonly causes **gastrointestinal upset**, including nausea, vomiting, taste disturbance, anorexia and diarrhoea.



This adverse effect may contribute to weight loss in patients taking metformin.

Side effects

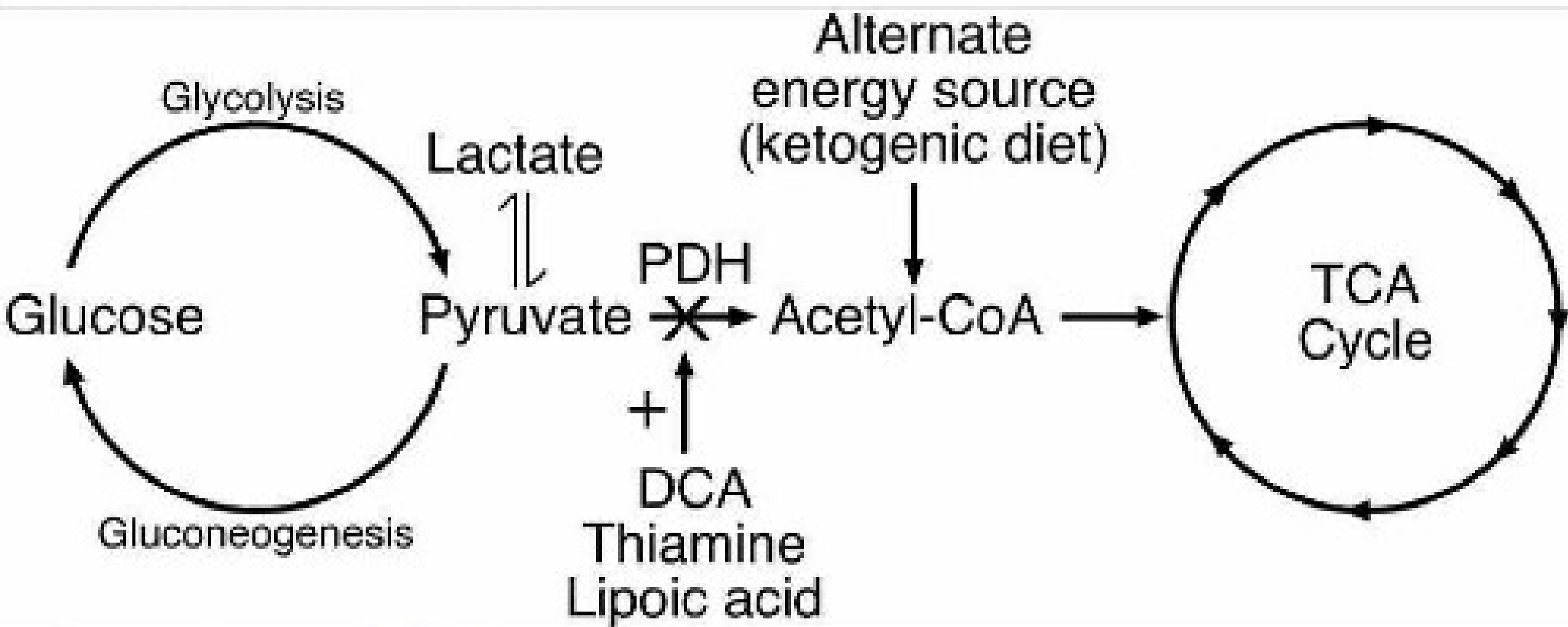
② **Lactic acidosis** is a rare adverse effect associated with metformin use, which can be fatal if untreated.

Note: Lactic acidosis does not occur in stable patients, but can be precipitated by associated illness that causes accumulation of metformin e.g.

- Worsening renal impairment
- Increased lactate production (e.g. sepsis, hypoxia, cardiac failure)
- Reduced lactate metabolism (e.g. liver failure).



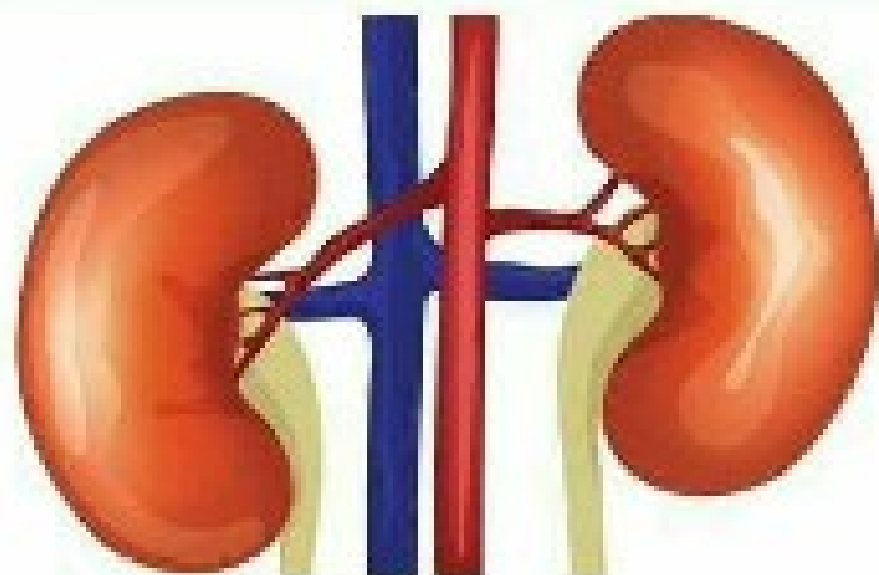
Side effects



Warnings

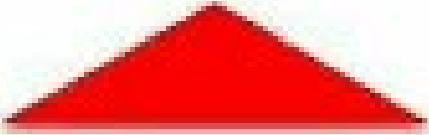
Metformin is excreted unchanged by the kidney. Metformin is therefore **contraindicated** in *severe renal impairment* and a dose reduction is required for patients with moderate renal impairment.

Metformin should be withheld acutely where there is acute kidney injury, e.g. in sepsis, shock, or dehydration; or severe tissue hypoxia, e.g. in cardiac or respiratory failure, or myocardial infarction.



Warnings

Caution is required in hepatic impairment as clearance of excess lactate may be impaired.



Metformin should be withheld during acute alcohol intoxication, when it may precipitate lactic acidosis, and be used with caution in chronic alcohol overuse, where there is a risk of hypoglycemia.

Drug interactions

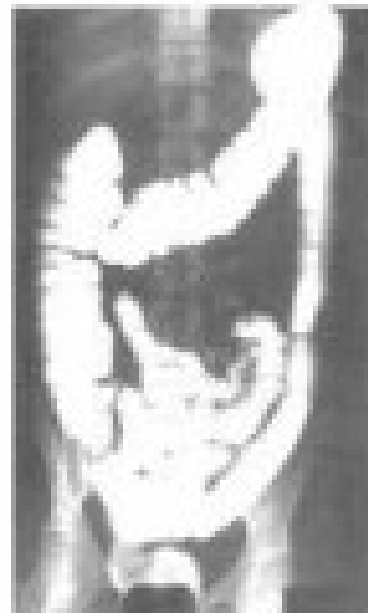
Metformin must be withheld before and for 48 hours after injection of IV contrast media.



e.g. CT scans and coronary angiography when there is an increased risk of renal impairment, metformin accumulation and lactic acidosis.



Without
CM



With
CM

Drug interactions

Other drugs (e.g. *ACE inhibitors, NSAIDs, diuretics*) with potential to **impair renal function** should also be used with caution (e.g. with renal function monitoring) in combination with metformin.



Drug interactions

Prednisolone, thiazide and loop diuretics elevate blood glucose, hence oppose the actions and reduce efficacy of metformin.



How to prescribe it

- ① Metformin is only available for **oral administration**.
- ② *Gastrointestinal adverse effects* of metformin are usually *transient* and are best tolerated if metformin is started at a low dose and increased gradually.
- ③ A common regimen is to start **metformin 500 mg once daily with breakfast**, increasing the dose by 500 mg weekly to 500–850 mg three times daily with meals.

STOP Metformin if adverse effects are intolerable or new contraindications develop.

Administration

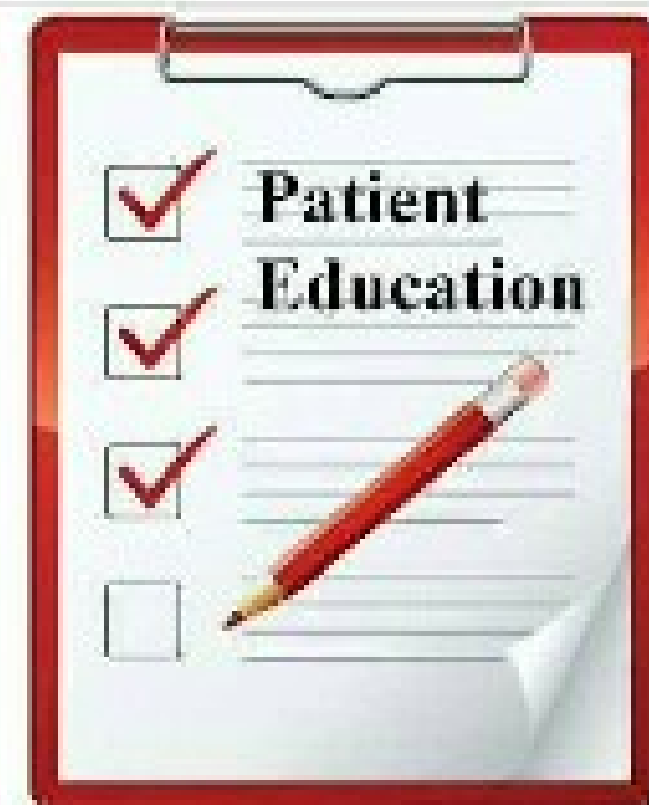
① Patients should be started on **a standard-release preparation of metformin** and advised to swallow tablets whole with a glass of water with or after food.



If gastrointestinal effects are intolerable, changing from standard to a modified-release preparation may help.

Patient education

Advise patients that metformin has been prescribed to **control the blood sugar level** and reduce the risk of diabetic complications, such as heart attacks.



Patient education

Explain that tablets are **not a replacement for lifestyle measures** and should be taken in addition to a calorie-controlled diet and regular exercise.



Patient education

Warn them to **seek urgent medical advice** if they experience vomiting, stomach ache, muscle cramps, difficulty breathing or severe tiredness, which may be symptoms of **lactic acidosis** (a very rare side effect).



Patient education

Advise them always to **tell the doctor** that they are taking metformin **before** having an **X-Ray with dye** or operation, as metformin may need to be stopped before the procedure.



Without
CM



With
CM

Monitoring of the treatment

- ➊ Assess blood glucose control by measuring glycated hemoglobin (**HbA1c**) (target <58 mmol/mol).
- ➋ **Blood glucose monitoring is not routinely required.**
- ➌ **Measure renal functions** before starting treatment, then at least annually.

The normal range for level for **hemoglobin A1c** is less than 6%

Note: Renal function should be measured more frequently (at least twice per year) in people with deteriorating renal function or at increased risk of renal impairment.

Clinical tip

Increasing **body weight** increases insulin resistance, which can worsen type 2 diabetes mellitus. Initial treatment for type 2 diabetes mellitus is therefore **calorie and carbohydrate restriction with increased physical activity**, which **should be tried for at least 3 months** before commencing drug therapy.



Clinical tip

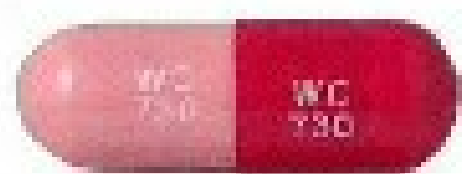
As **insulin is an anabolic hormone**, it and drugs which increase insulin secretion (e.g. sulphonylureas) cause weight gain, which can worsen diabetes mellitus over the long term. **Metformin**, which does not cause weight gain, is therefore usually **the first choice treatment** unless contraindicated.



Penicillins

Broad-spectrum

Amoxicillin
Co-amoxiclav

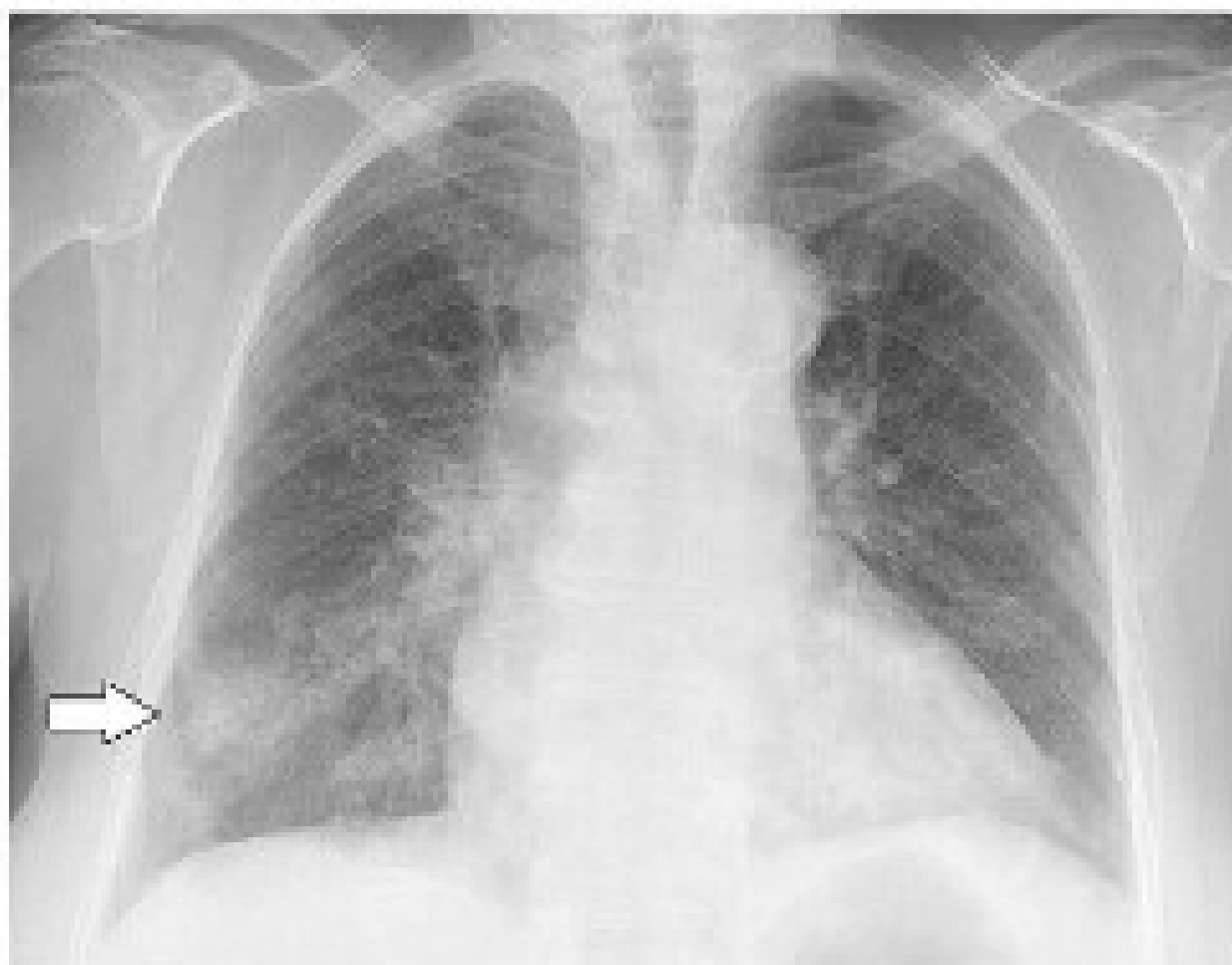


WC 730



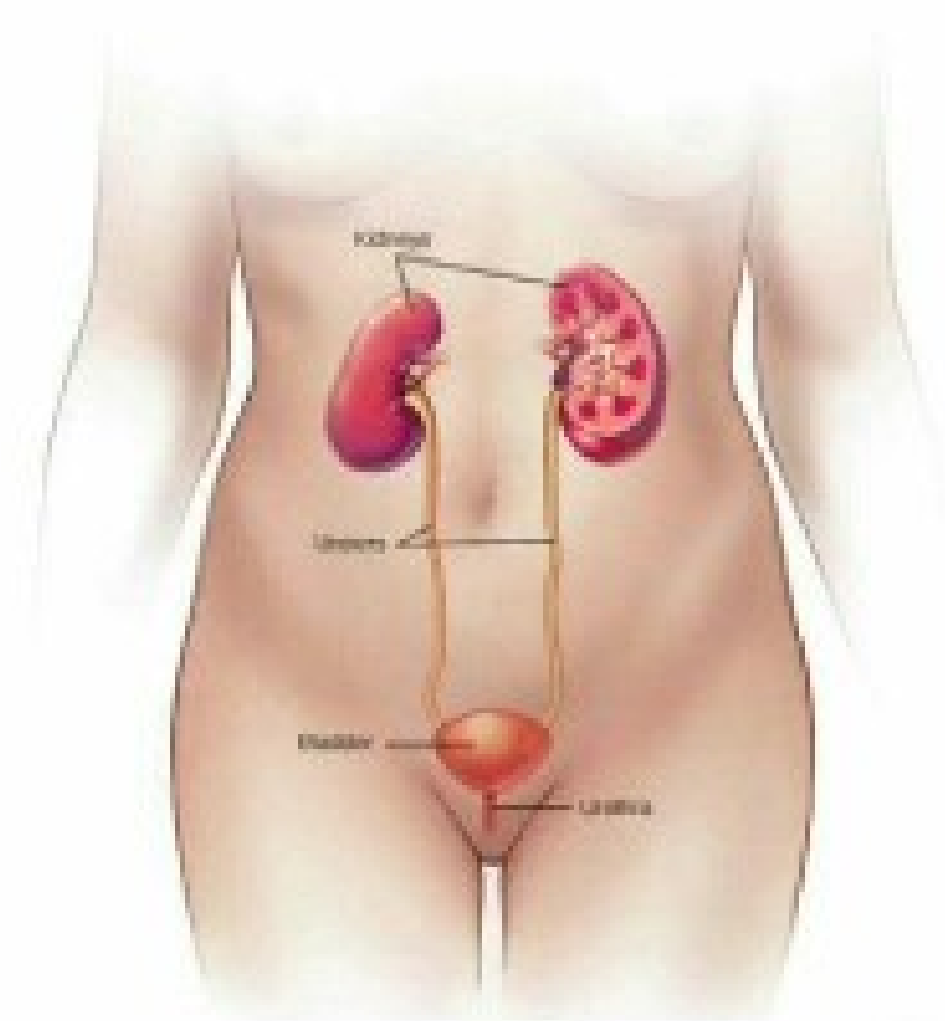
Indications

❶ Empirical treatment of pneumonia, which may be caused by Gram-positive (e.g. ***Streptococcus pneumoniae***) or Gram-negative pathogens (e.g. ***Haemophilus influenzae***).



Indications

② Empirical treatment of **urinary tract infection** (most commonly caused by *Escherichia coli*).



Trimethoprim and Nitrofurantoin are alternatives.

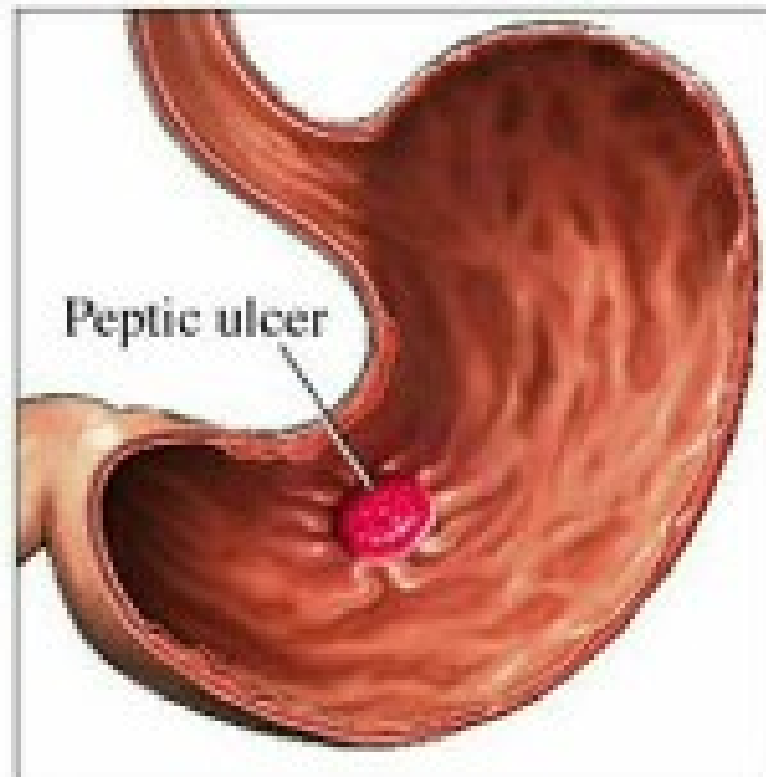
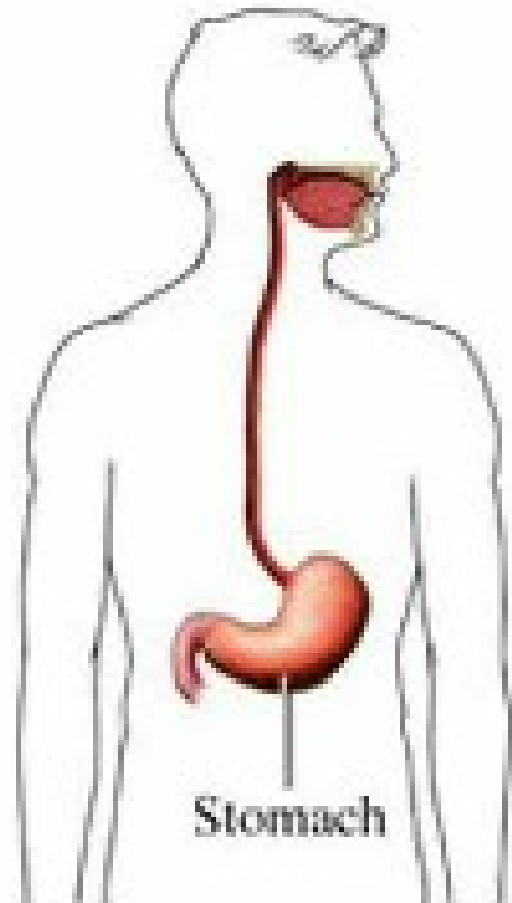
Indications

③ As part of **combination treatment** (as co-amoxiclav) for **hospital-acquired infection or intra-abdominal sepsis**, which may be caused by Gram-negative and anaerobic pathogens or antibiotic-resistant organisms.



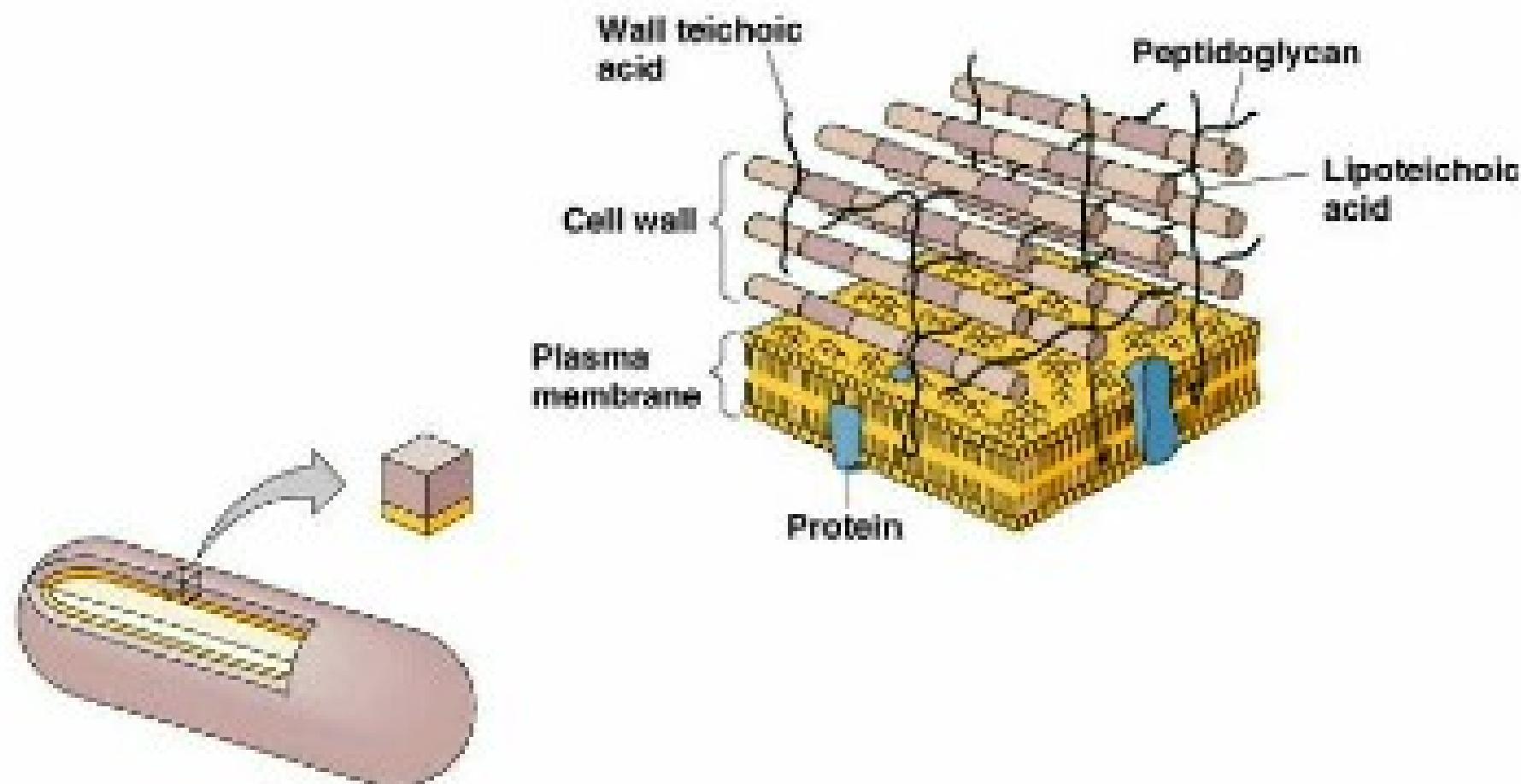
Indications

- ④ As part of combination treatment for **H. pylori-associated peptic ulcers**.



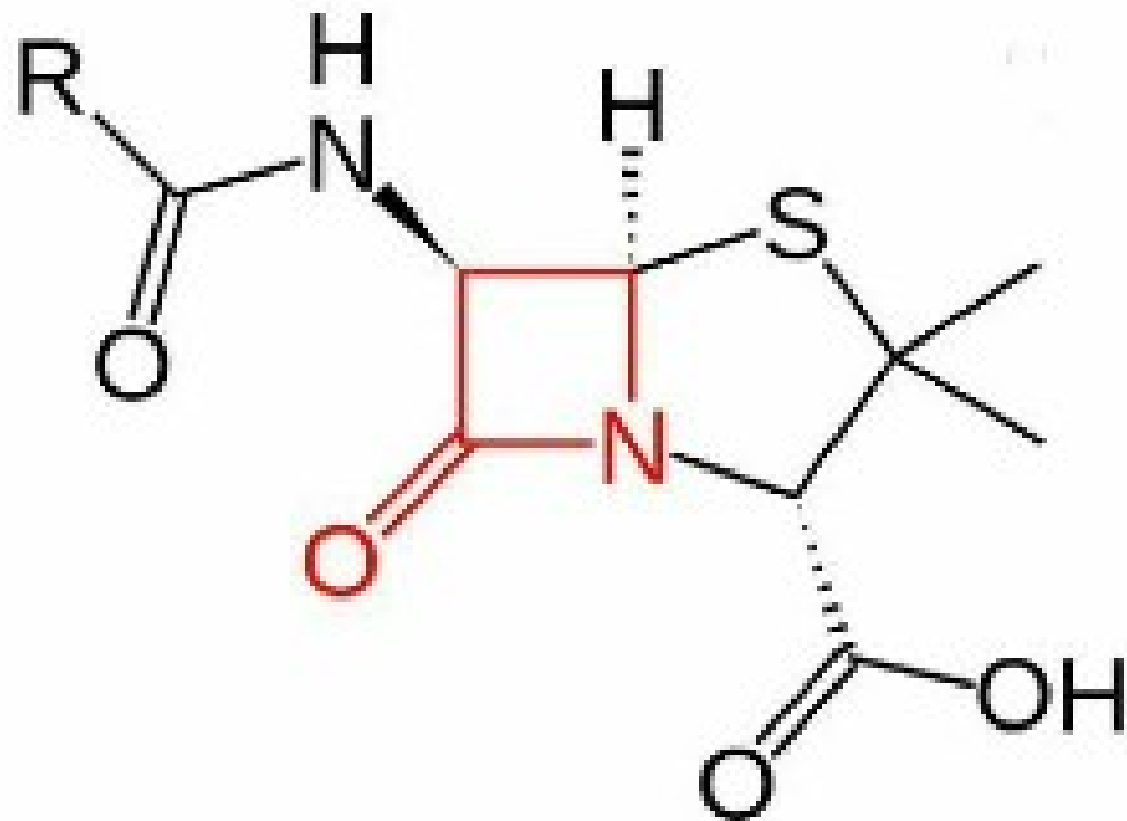
Mechanism of action

① Penicillins inhibit **cross-linking peptidoglycans in bacterial cell walls**. This weakens cell walls, preventing them from maintaining an osmotic gradient. Uncontrolled entry of water into bacteria causes cell swelling, lysis and death.



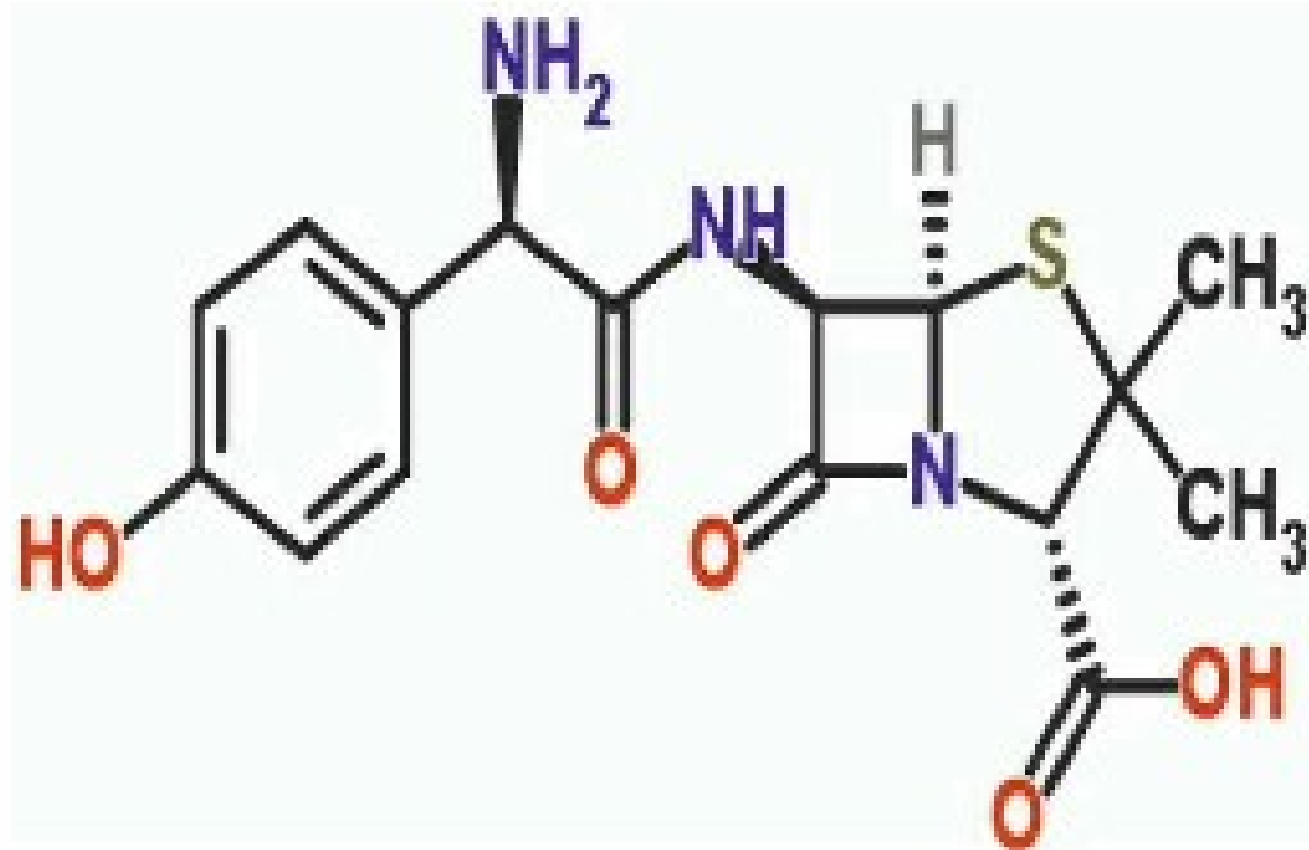
Mechanism of action

② Penicillins contain a **β -lactam ring**, which is responsible for their *antimicrobial activity*. Side chains attached to the β -lactam ring can be modified to make semi-synthetic penicillins.



Mechanism of action

③ For **amoxicillin**, addition of an **Amino group** to the side chain increases activity against aerobic Gram -ve bacteria, making this a 'broad-spectrum' antibiotic.



Mechanism of action

④ Addition of the **β -lactamase inhibitor Clavulanic acid** (creating co-amoxiclav) increases the spectrum of antimicrobial activity further to include β -lactamase-producing bacteria (e.g. *Staphylococcus aureus*, Gram-negative anaerobes).



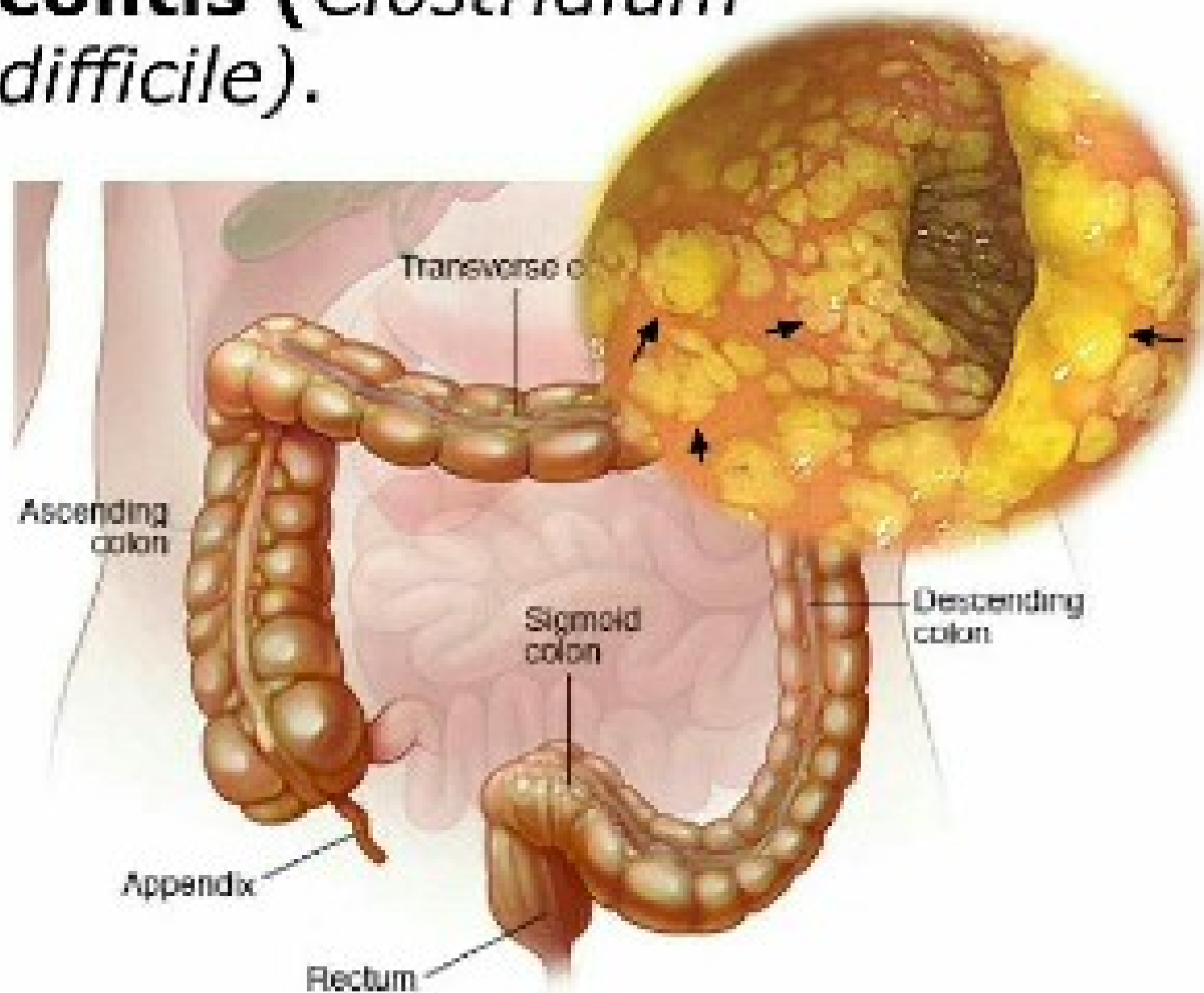
Side effects

① **Gastrointestinal upset** such as nausea and diarrhoea are common.



Side effects

② Less frequently, **antibiotic-associated colitis** (*Clostridium difficile*).



Marked exudate protruding through an area of mucosal ulceration (**Volcano lesion**)

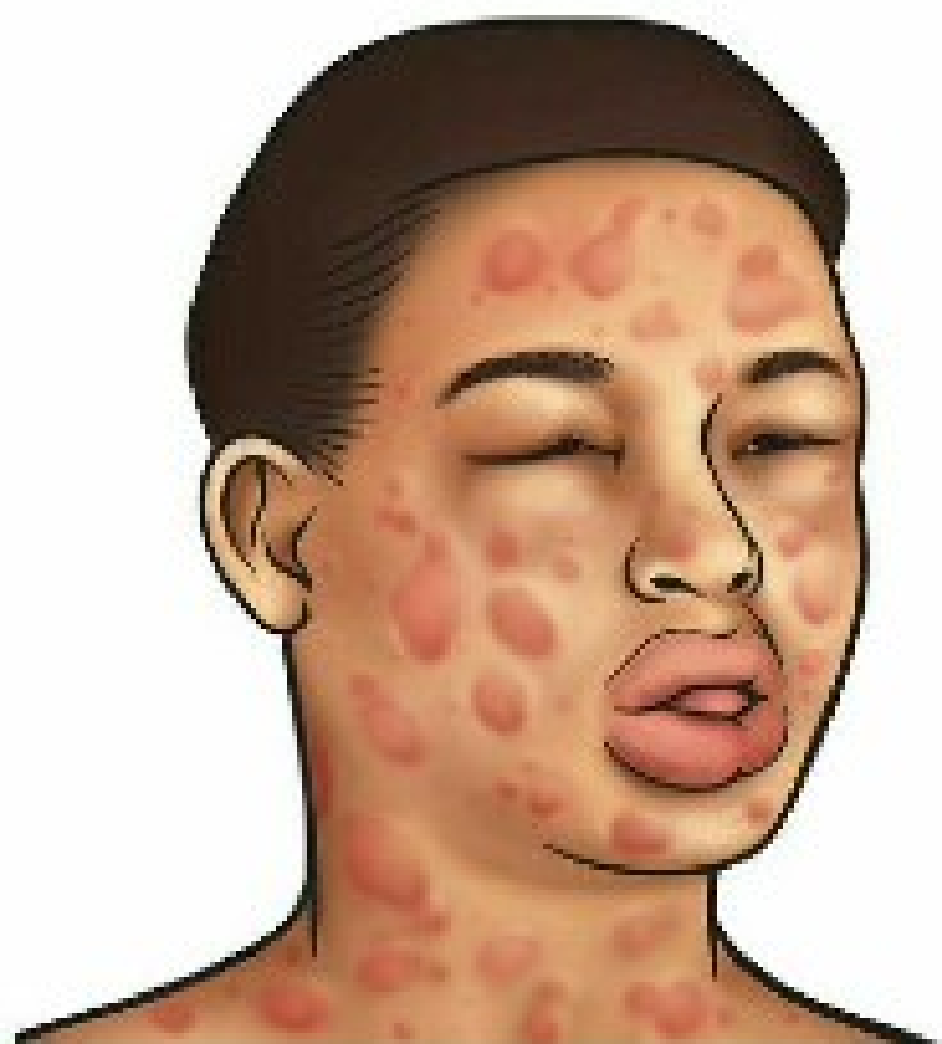
Side effects

③ **Penicillin allergy** affects 1–10% of people. This usually presents as a skin rash 7–10 days after first or 1–2 days after repeat exposure (**delayed IgG-mediated reaction**).



Side effects

④ Less commonly, an immediate (minutes to hours) life-threatening IgE-mediated **anaphylactic reaction** occurs with features including hypotension, bronchospasm and **angioedema**.



Side effects

⑤ **Cholestatic jaundice** is a rare adverse effect of co-amoxiclav.

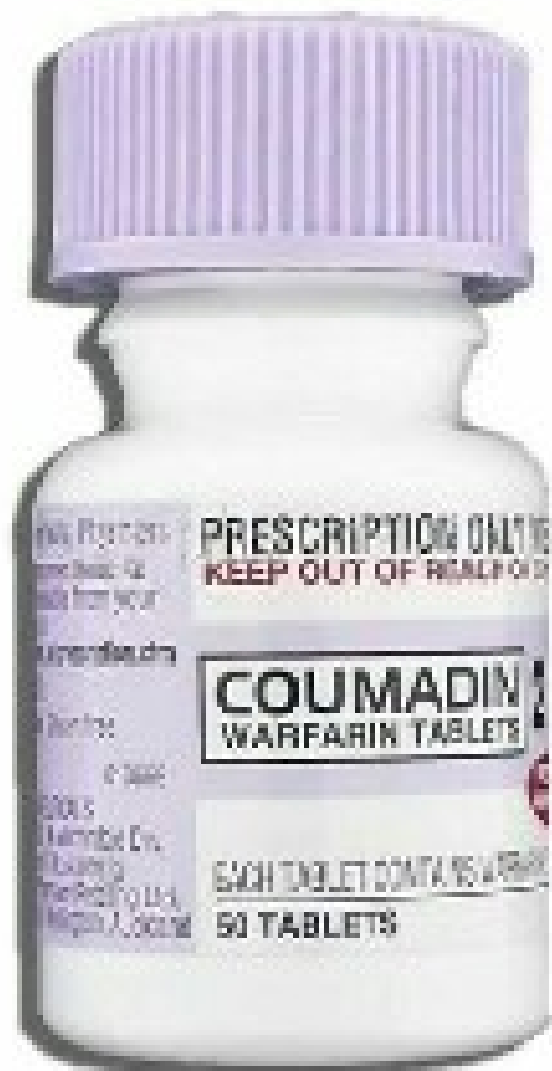


Drug interactions



Penicillins reduce renal excretion of **Methotrexate**, increasing the **Risk of toxicity**.

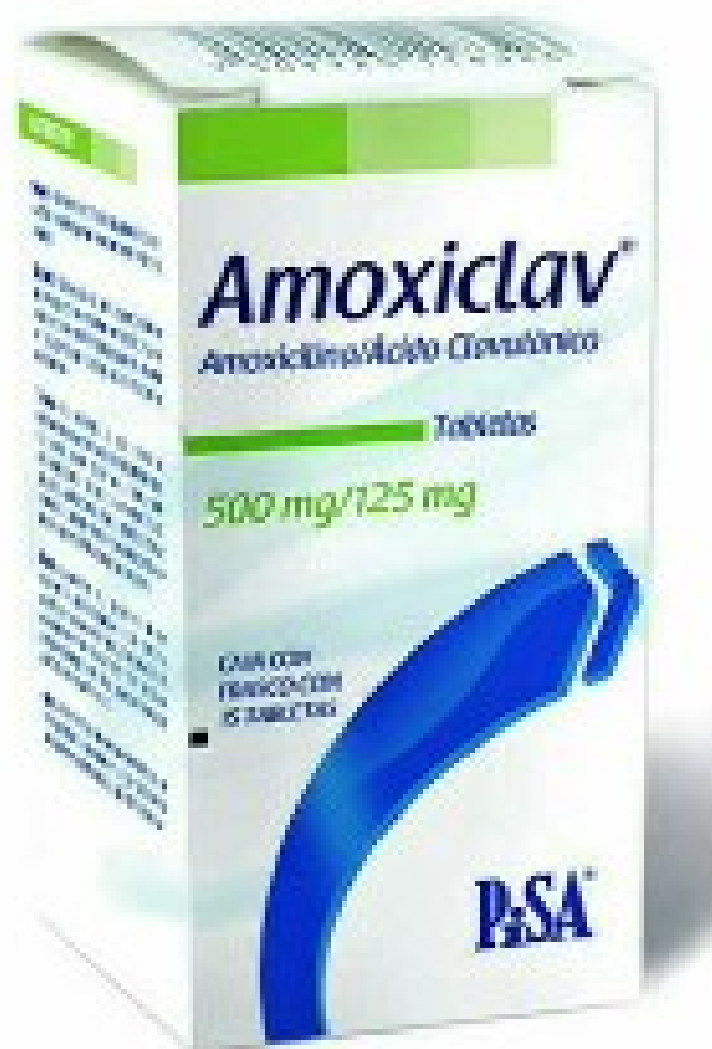
Drug interactions



Broad-spectrum penicillins can **enhance** the anticoagulant effect of **Warfarin** by killing normal gut flora that synthesize vitamin K. This increases **Risk of bleeding.**

How to prescribe it

① For **mild-to-moderate infection** (e.g. without systemic features) **Oral amoxicillin** should be prescribed at a lower dose (e.g. 250–500 mg 8-hrly).



How to prescribe it

② For **severe infection**, amoxicillin is prescribed at a high dose for **IV administration** (e.g. 1 g 8-hrly).

Note: Prompt IV-to-oral switch reduces complications and costs of antibiotic treatment and facilitates early discharge.



How to prescribe it

③ Intravenous antibiotics should be **switched to oral administration** *after* 48 hours if clinically indicated and the patient is improving (e.g. resolution of pyrexia, tachycardia) and able to take oral medication.



How to prescribe it

④ When writing an *inpatient* prescription for antibiotics, it is essential to include the **indication** and **duration of treatment** to promote review and ensure good antibiotic therapy.

Administration



Advise your patient to take the medicine
(e.g. Augmentin
®: amoxicillin/clavulanate
potassium) Tablets, Powder for
Suspension, or Chewable Tablets
at the start of a meal to reduce
stomach upset.

Patient education

- Explain that the aim of treatment is to get rid of infection and improve symptoms.



Patient education

- For oral treatment, encourage the patient to **complete the prescribed course.**



Patient education

- Before prescribing, always check with your patient personally or get collateral history to ensure that they do not have an **allergy** to any form of penicillin or other β -lactam antibiotics.



Administration

Stop using this medicine and call your doctor at once if you have a serious side effect such as:

- 1 Diarrhea that is watery or has blood in it.
- 2 Pale or yellowed skin, dark colored urine, fever, confusion or weakness.
- 3 Easy bruising or bleeding.
- 4 Skin rash, bruising, severe tingling, numbness, pain, muscle weakness.
- 5 Agitation



Patient education

- If **allergy** developed during treatment, give the patient **written and verbal advice** not to take this antibiotic in the future and make sure that the allergy is clearly documented in their medical records.



Monitoring of the treatment

Check that infection resolves by resolution of symptoms, signs (e.g. pyrexia, lung crackles) and blood markers (e.g. falling C-reactive protein and white cell count) as appropriate.

Clinical tip

Individual hospitals have **antibiotic policies** to reduce the risk of hospital-acquired infection. These include limiting the use of broad-spectrum antibiotics such as amoxicillin/co-amoxiclav where there is a narrower spectrum alternative. For example, they may recommend benzylpenicillin rather than amoxicillin for pneumonia alongside clarithromycin.

Always follow your local antibiotic guidelines and seek microbiology advice as needed.



Proton Pump Inhibitors (PPI)

Lansoprazole
Omeprazole
Pantoprazole



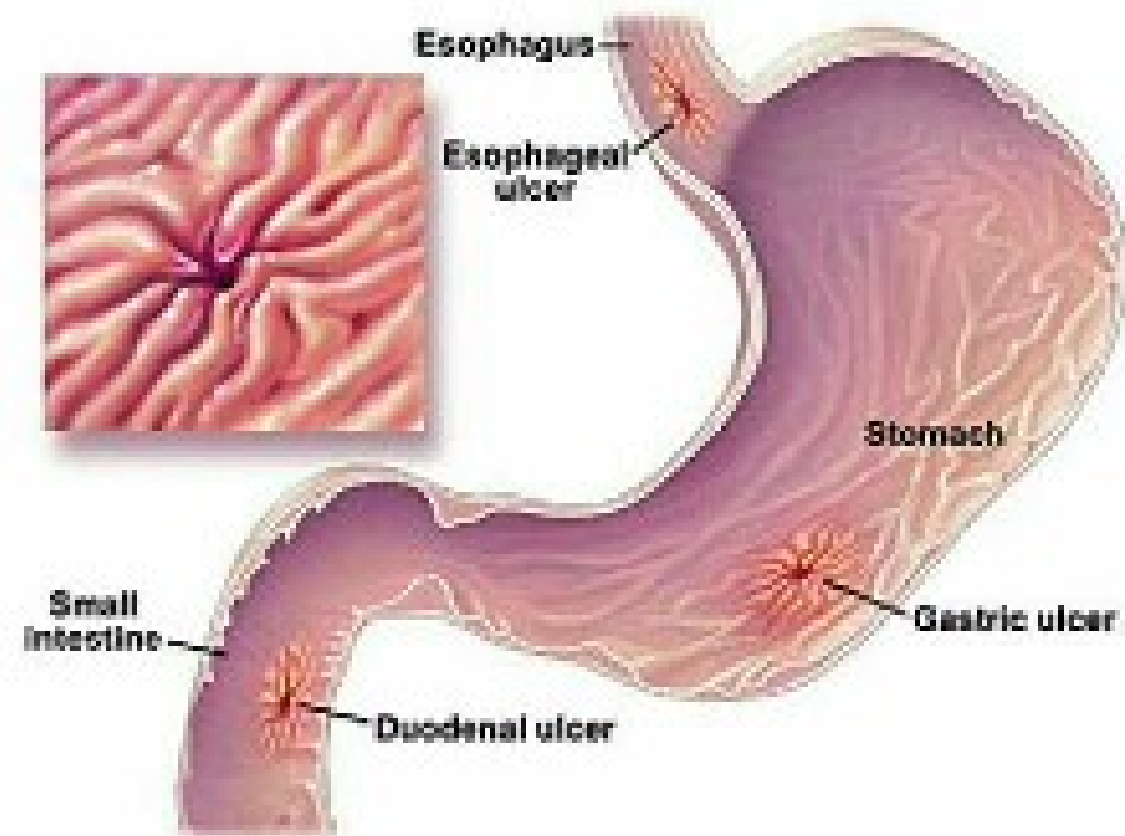
Indications

Proton pump inhibitors are a first-line treatment for:

❶ Prevention and treatment of **peptic ulcer disease**, including NSAID-associated ulcers.

❷ Symptomatic relief of **dyspepsia** and gastro-esophageal reflux disease.

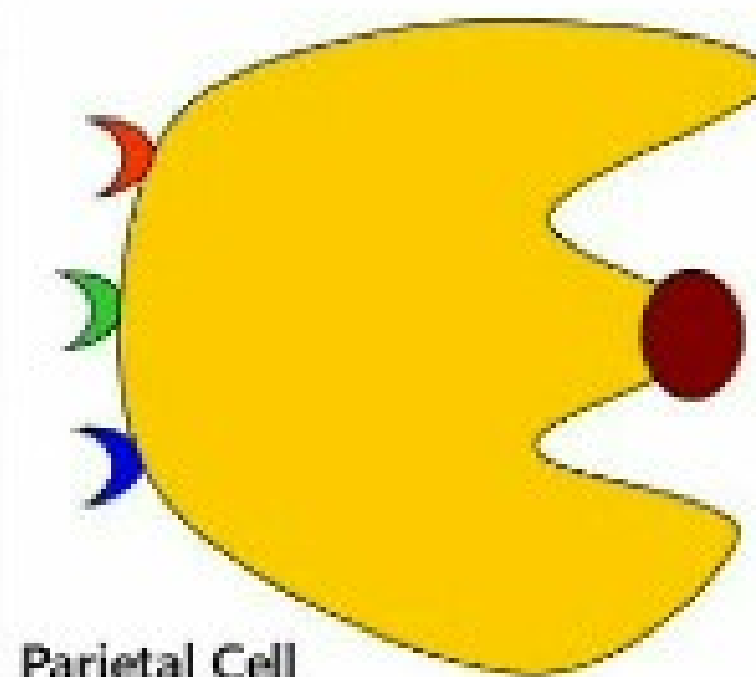
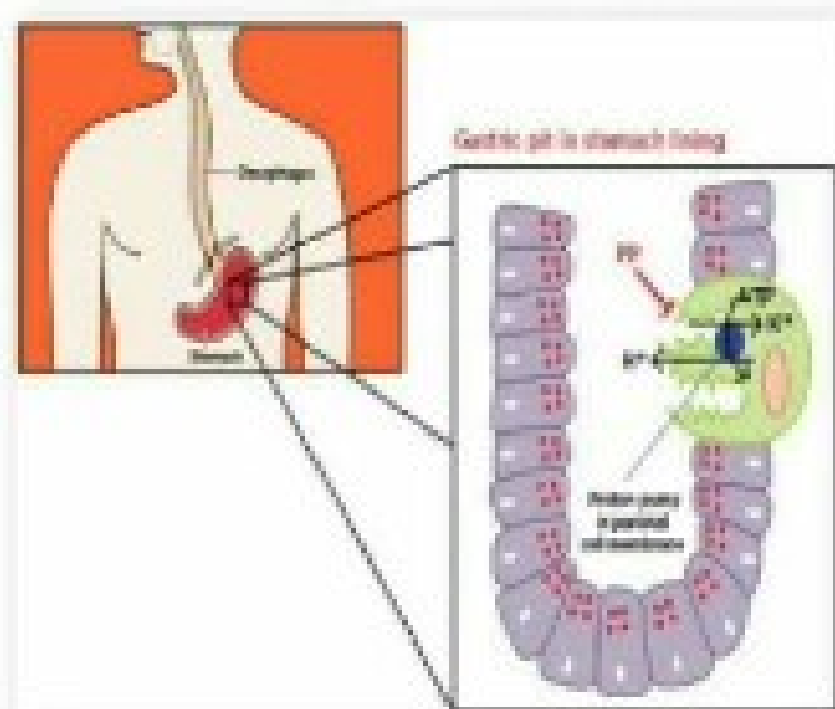
❸ Eradication of ***Helicobacter pylori* infection**, in which they are used in combination with antibiotic therapy.



Mechanism of action

Proton pump inhibitors (PPIs) reduce gastric acid secretion.

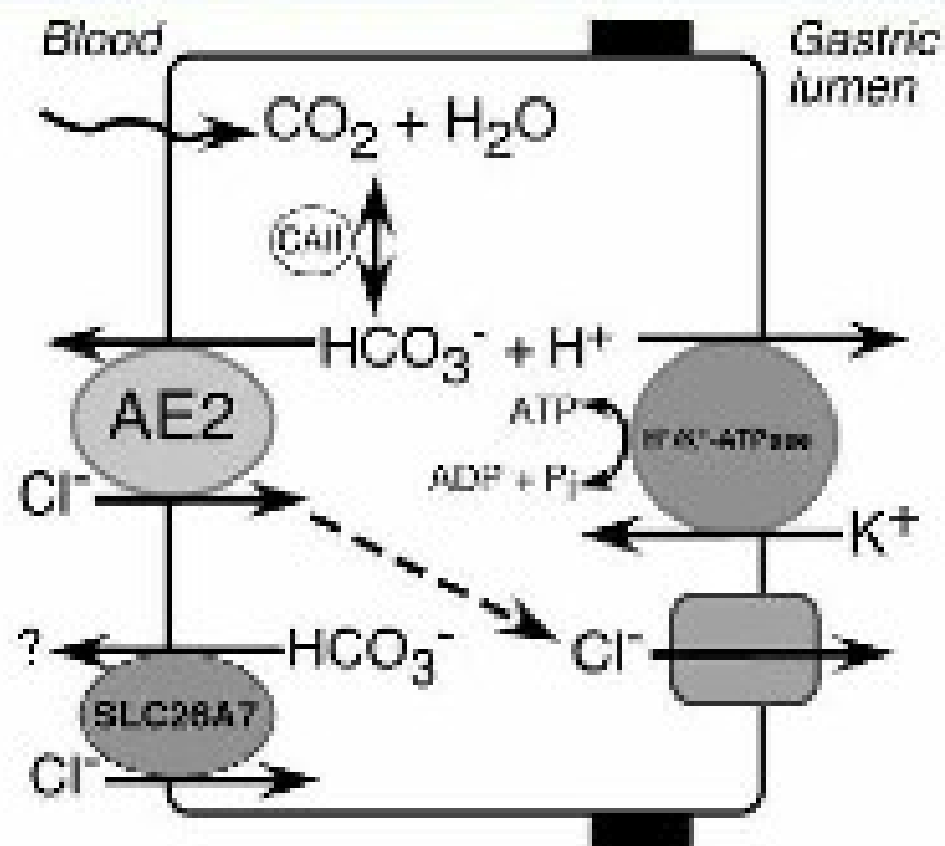
They act by irreversibly **inhibiting $H^+/K^+-ATPase$** in gastric parietal cells. This is the 'proton pump' responsible for secreting H^+ and generating gastric acid.

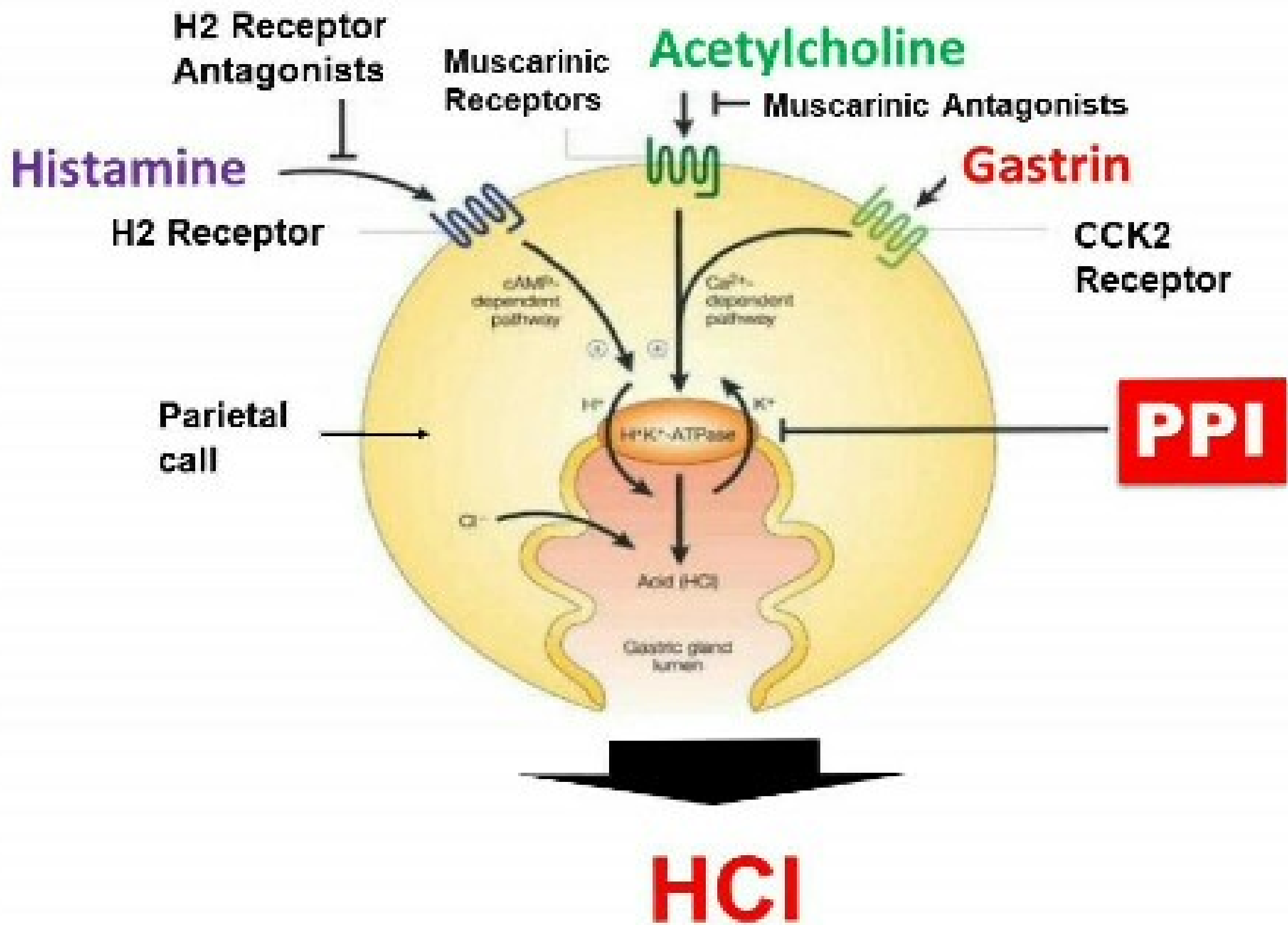


Mechanism of action

An advantage of **targeting the final stage of gastric acid production** is that they are able to **suppress gastric acid production almost completely**.

In this respect they differ from H₂-receptor antagonists.





Side effects

- ① Common side effects of PPIs include **GIT disturbances** and **headache**.
- ② By increasing the gastric pH, PPIs may reduce the body's host defense against infection; there is some evidence of **Increased risk of Clostridium difficile infection** in patients taking PPIs.
- ③ Prolonged treatment with PPIs can cause **Hypomagnesaemia**, which if severe can lead to tetany and ventricular arrhythmia.



PPI inhibits Mg absorption via influencing a second magnesium transport system (TRPM) cation channels.

Warnings

PPIs may mask symptoms of gastric cancer, so prescribers should enquire about '**alarm symptoms**' before and during treatment.

There is epidemiological evidence that PPIs, particularly when administered at high dose for prolonged courses in the elderly, can **increase the risk of fractures**



Note: Patients at risk of osteoporosis should therefore be identified and treated as appropriate).

Drug interactions



There is some evidence that PPIs, particularly **Omeprazole**, **reduce the antiplatelet effect of clopidogrel** by decreasing its activation by cytochrome P450 enzymes.

Current evidence suggests that **Lansoprazole** and **Pantoprazole** have a lower tendency to interact with clopidogrel
(?! Preferred PPIs when prescribing alongside clopidogrel).

How to prescribe it

Generally the **lowest** effective dose of PPIs should be used for the **shortest** period possible.



Administration

Oral preparations can be taken with food or on an empty stomach.

They are best taken in the **morning**.



Intravenous preparations should be given by slow injection or infusion.

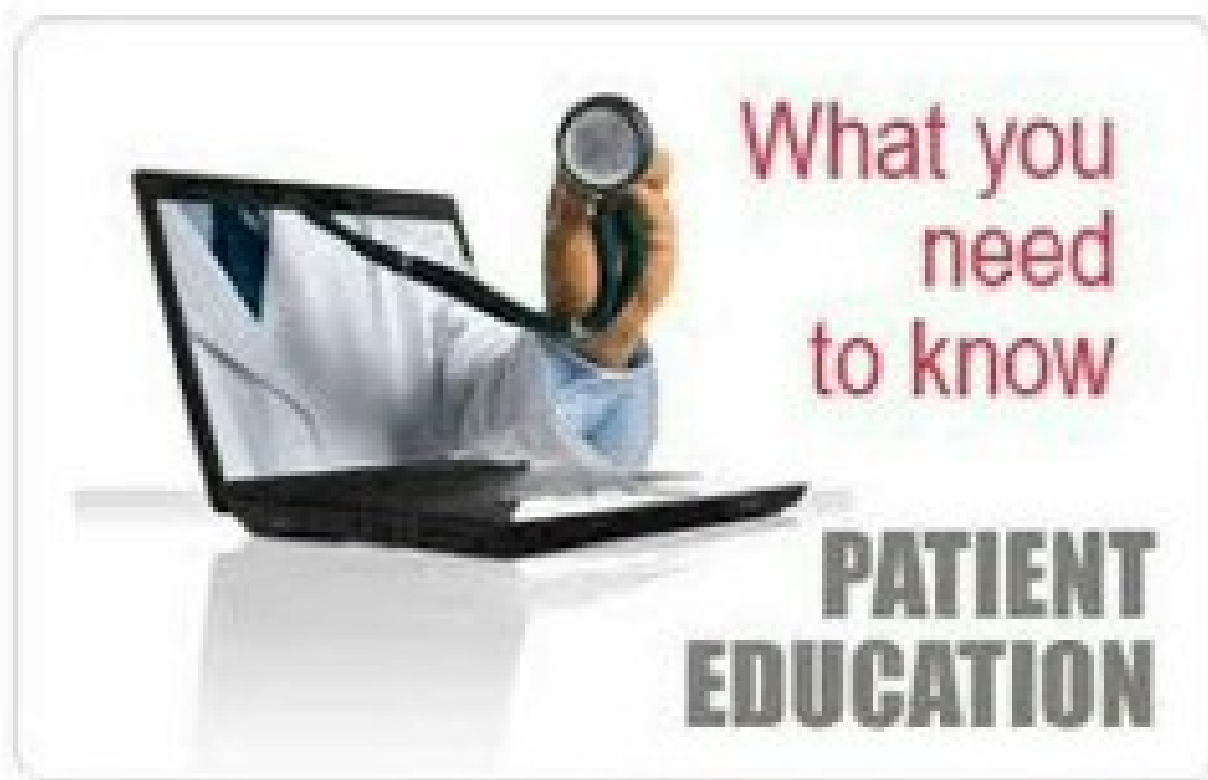
Patient education

Explain that you are offering treatment to reduce stomach acid. This will hopefully improve their symptoms and, if applicable, allow their ulcer to heal.



Patient education

Ensure that both you and the patient are clear on the **intended duration of therapy** (e.g. a 7-day course to eradicate *H. pylori*, or long-term therapy to protect against ulcers) and **how success will be judged** (e.g. evidence of healing on endoscopy, or simply by resolution of symptoms).



Patient education

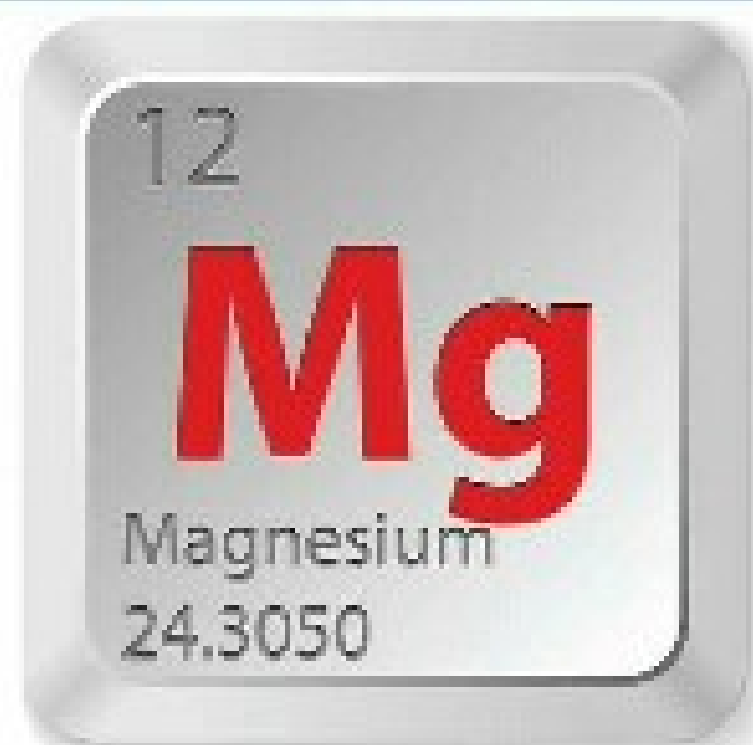
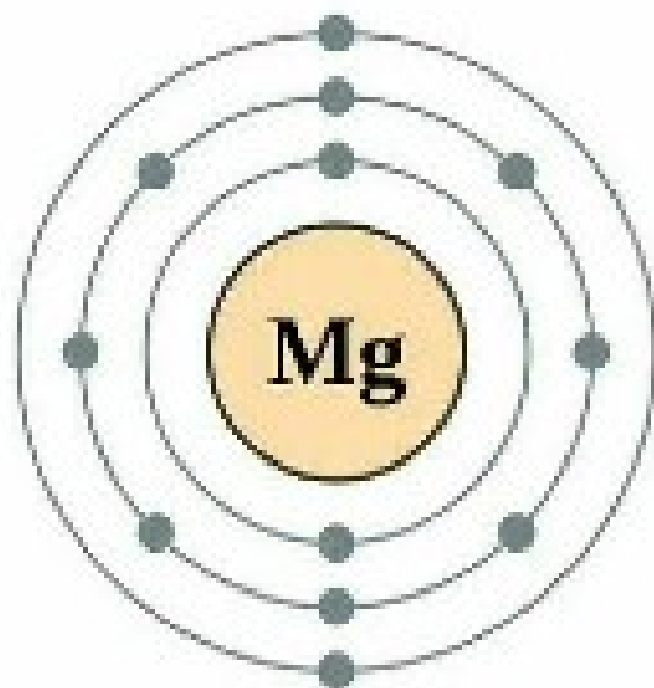
Ask the patient to report any problems, particularly '**alarm symptoms**' (e.g. severe pain, weight loss, vomiting).



Monitoring of the treatment

Response to treatment should be monitored in terms of **symptomatic response** and, in some cases (e.g. peptic ulcers), endoscopic appearance.

In prolonged use (>1 year) you should check serum magnesium levels due to the risk of hypomagnesaemia.

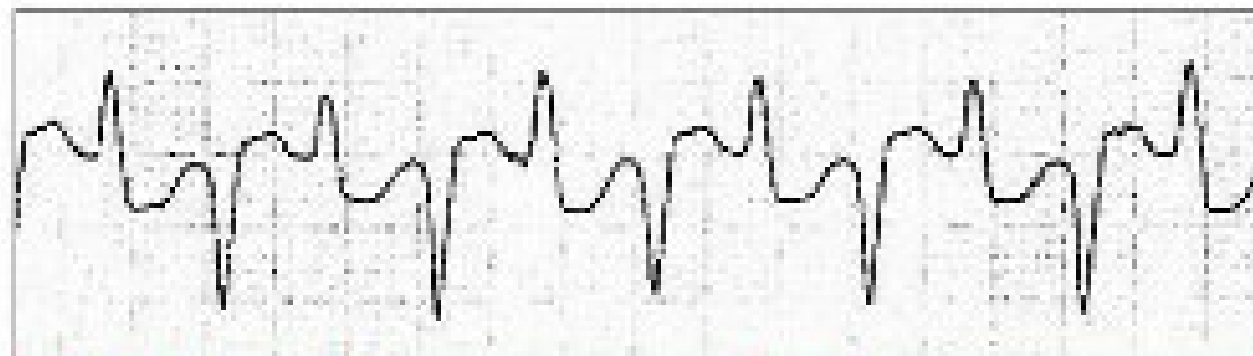
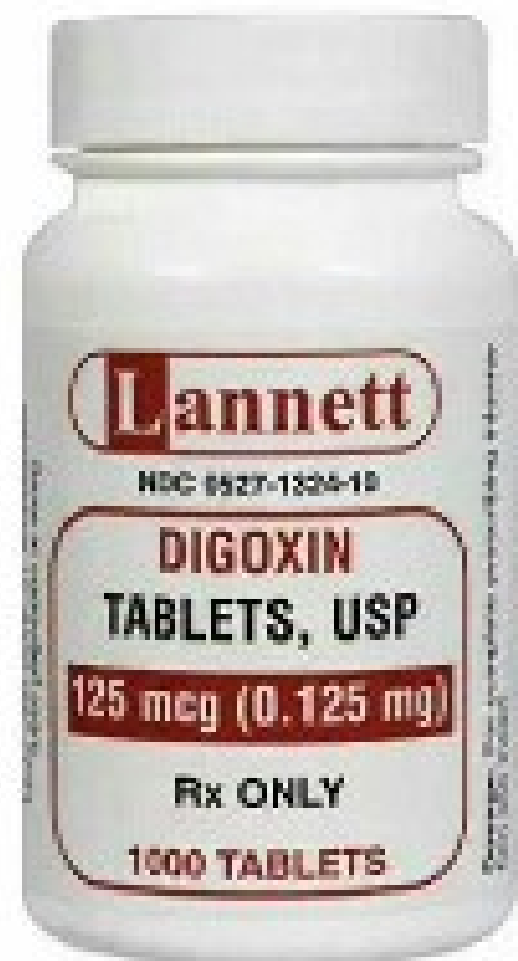


Clinical tip

Patients undergoing **investigation for H. pylori infection** should *ideally* stop their PPI **for 2 weeks before testing**. This is because it increases the chance of a false negative result.



PPIs such as Esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole were shown to slightly **increase the absorption of digoxin**, raising its blood levels and promoting its tendency toward cardiac arrhythmia.

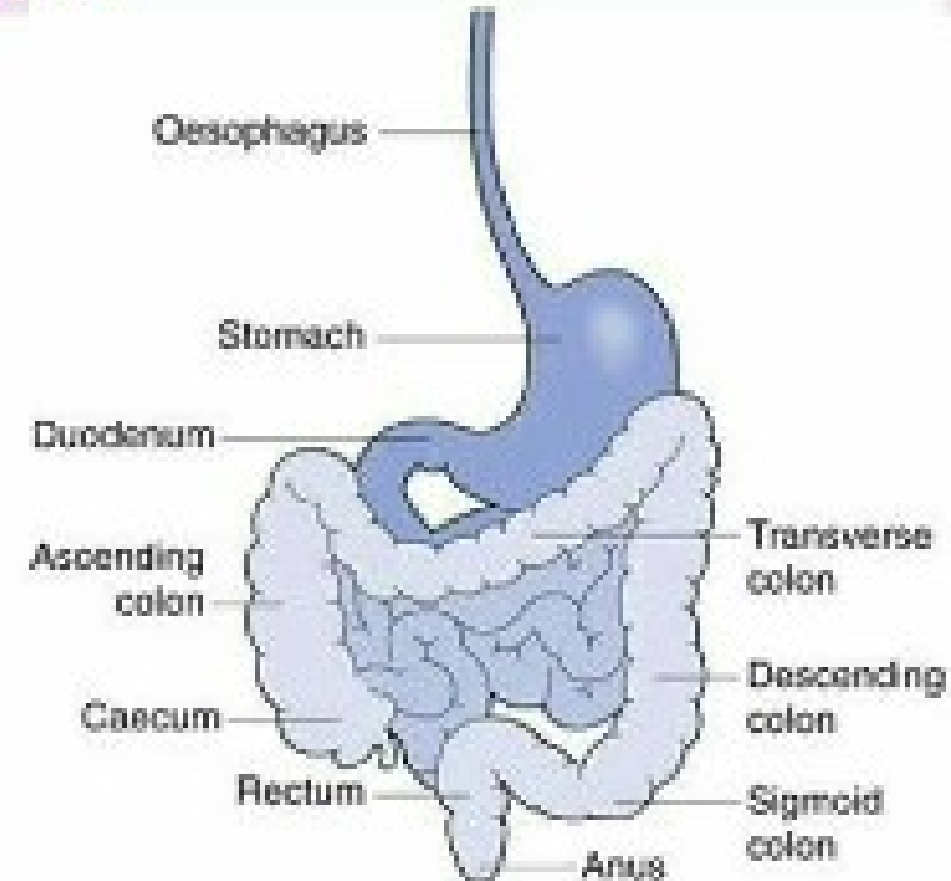


PPIs increase the absorption of digoxin

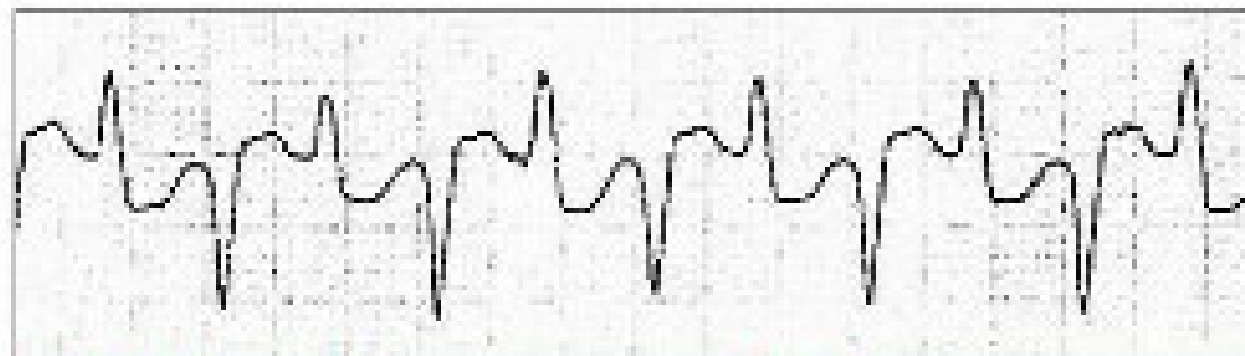
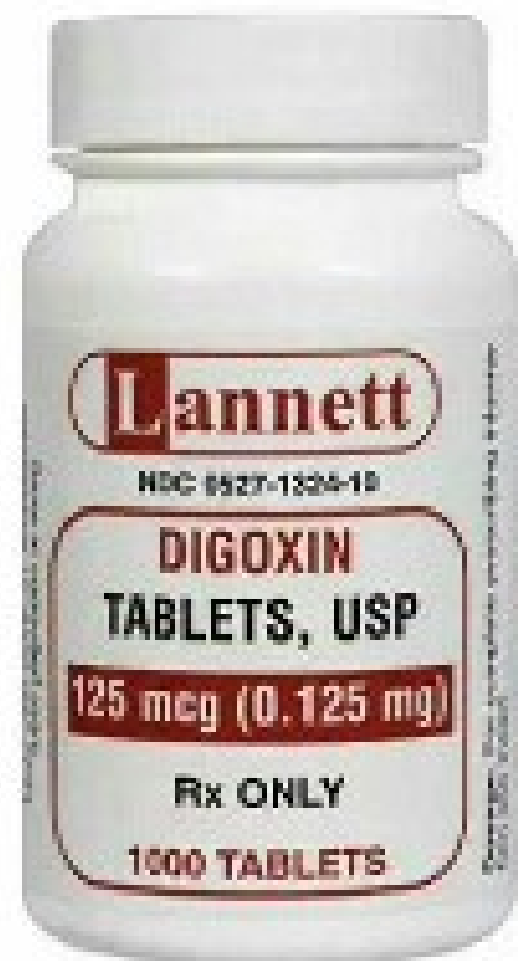


Proton-pump inhibitors can reduce the acidity of stomach fluid, decreasing the intestinal absorption of many drugs. Those drugs include

Allopurinol (an antigout drug)
Cyanocobalamin (vitamin B-12)
Diazepam
Glucocorticoids
Isoniazid (an antituberculous drug)
Iron salts
Ketoconazole (an antifungal drug)
Penicillamine (a metal chelator)
Phenothiazine antipsychotic drugs
Phenytoin (an antiepileptic drug)
Protease inhibitors such as amprenavir, atazanavir, and tipranavir
Quinolone antibiotics such as ciprofloxacin, levofloxacin, norfloxacin
Tetracyclines such as doxycycline, minocycline, and tetracycline



PPIs such as Esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole were shown to slightly **increase the absorption of digoxin**, raising its blood levels and promoting its tendency toward cardiac arrhythmia.



PPIs increase the absorption of digoxin



Diuretics Thiazide and Thiazide-like

Bendroflumethiazide
Indapamide
Chlortalidone



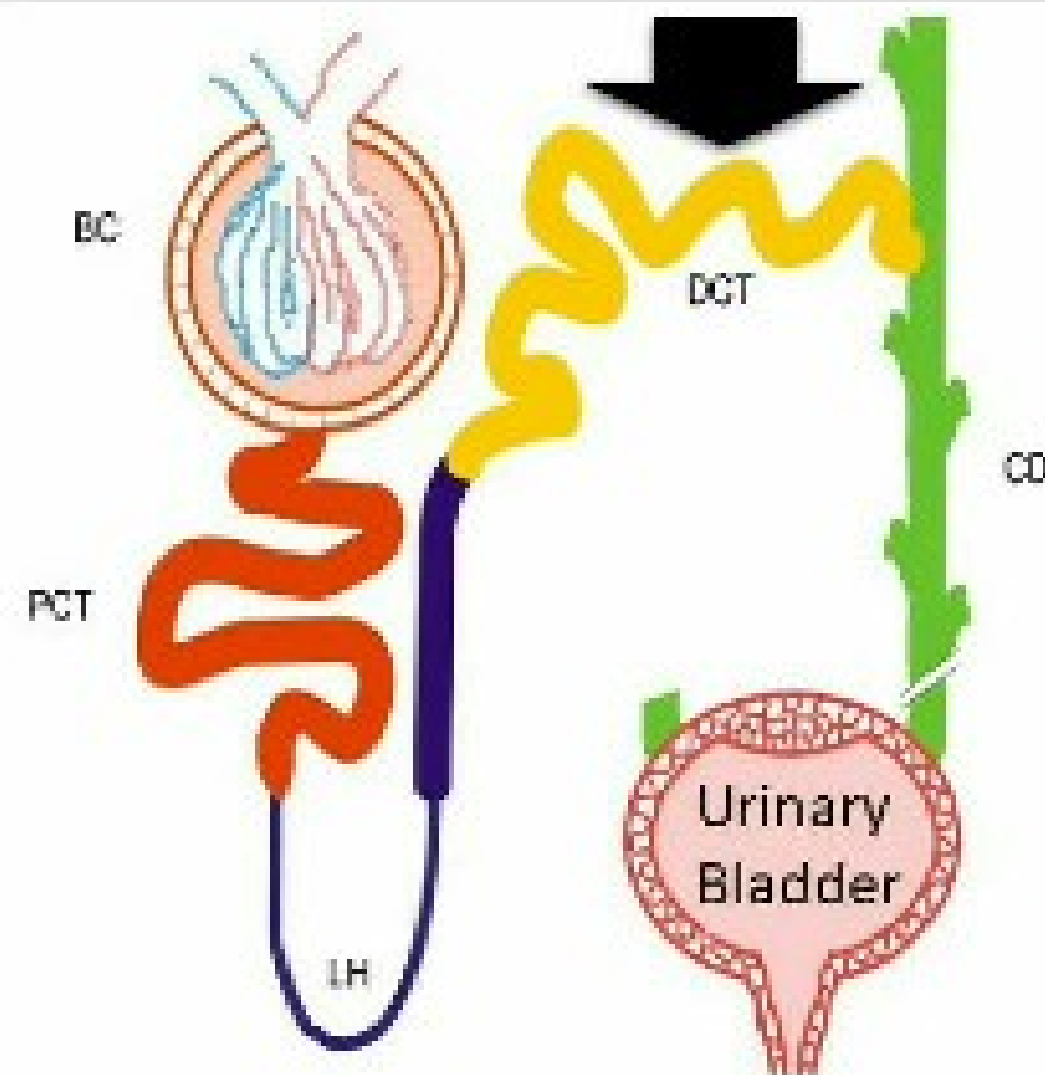
Indications

① Thiazides are an **alternative first-line treatment for hypertension** where a calcium channel blocker would otherwise be used, but is either unsuitable (e.g. due to oedema) or there are features of heart failure.

② Thiazides are also an **add-on treatment for hypertension** in patients whose blood pressure is not adequately controlled by a calcium channel blocker plus an ACE inhibitor or angiotensin receptor blocker (ARB).

Mechanism of action

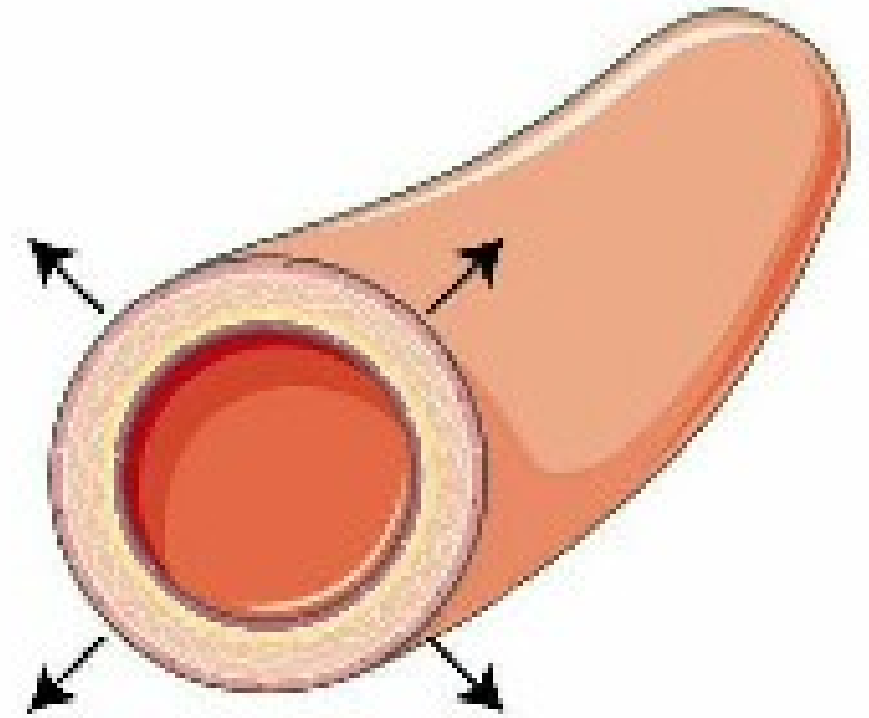
Thiazides inhibit the Na^+/Cl^- co-transporter in the distal convoluted tubule of the nephron. This prevents reabsorption of sodium and its osmotically associated water. The resulting diuresis causes an initial fall in extracellular fluid volume.



Note: Over time, compensatory changes (e.g. activation of the renin-angiotensin system) tend to reverse this, at least in part.

Mechanism of action

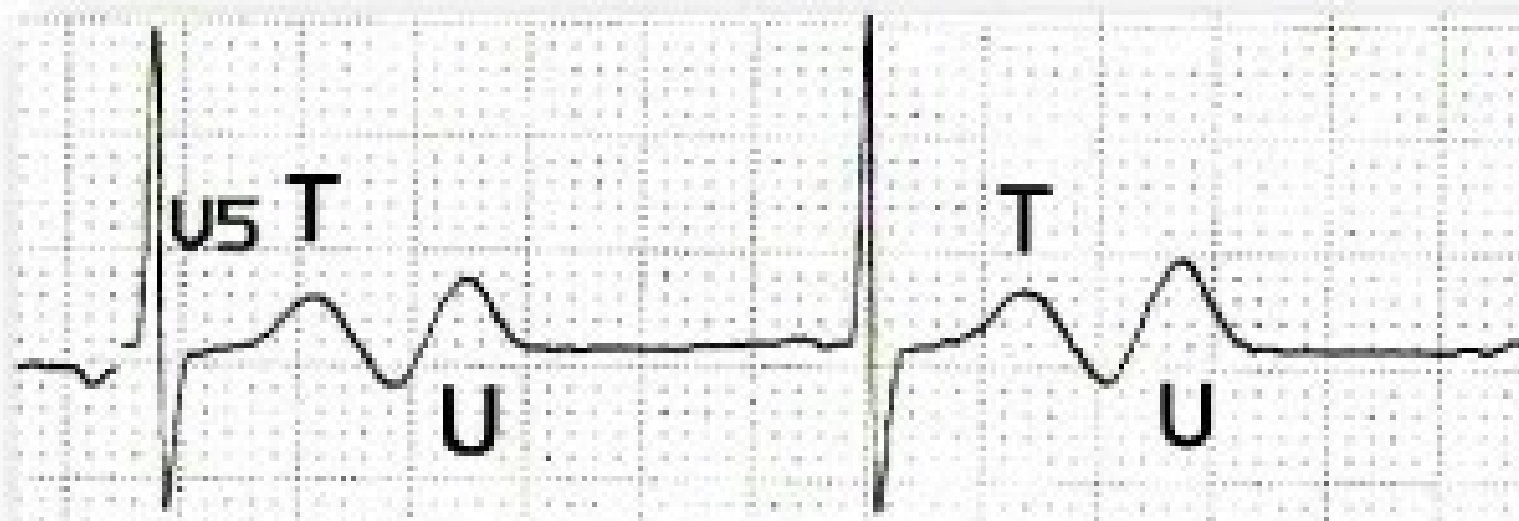
The long-term antihypertensive effect is probably mediated by ***Vasodilatation*** (a mechanism of which is incompletely understood).



Side effects

Preventing sodium reabsorption from the nephron can cause **Hyponatremia** (usually not problematic).

The increased delivery of sodium to the distal tubule, where it can be exchanged for potassium, increases urinary potassium losses and may therefore cause **Hypokalemia**.



Side effects

Thiazides may increase plasma concentrations of glucose (which may unmask type 2 diabetes), LDL-cholesterol and triglycerides. However, their net effect on cardiovascular risk is protective.



Side effects

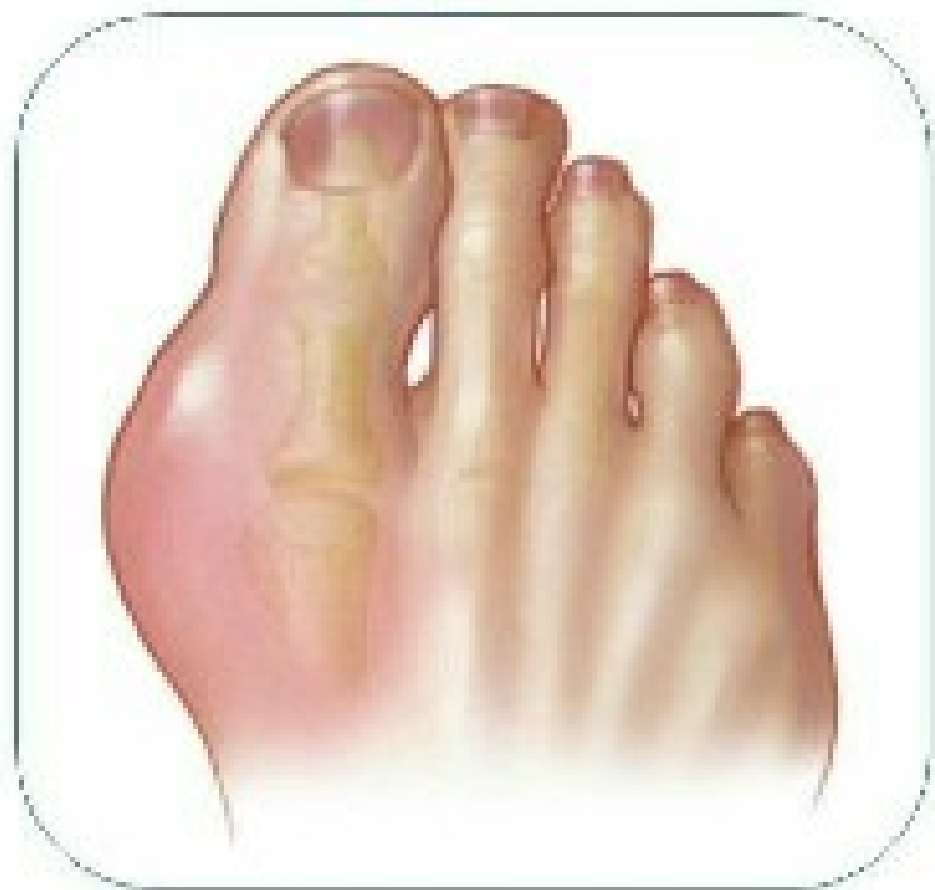
They may cause **impotence** in men.



Warnings

Thiazides should be **avoided** in patients with hypokalemia and hyponatremia.

As they reduce uric acid excretion, they may precipitate acute attacks in patients with **Gout**.



Drug interactions

- ① The effectiveness of thiazides may be reduced by **NSAIDs** (although low-dose aspirin is not a concern).
- ② The **combination** of thiazides with other drugs that lower the serum potassium concentration (e.g. loop diuretics) is best avoided



Note: If combination is essential- It should prompt intensive electrolyte monitoring).

How to prescribe it

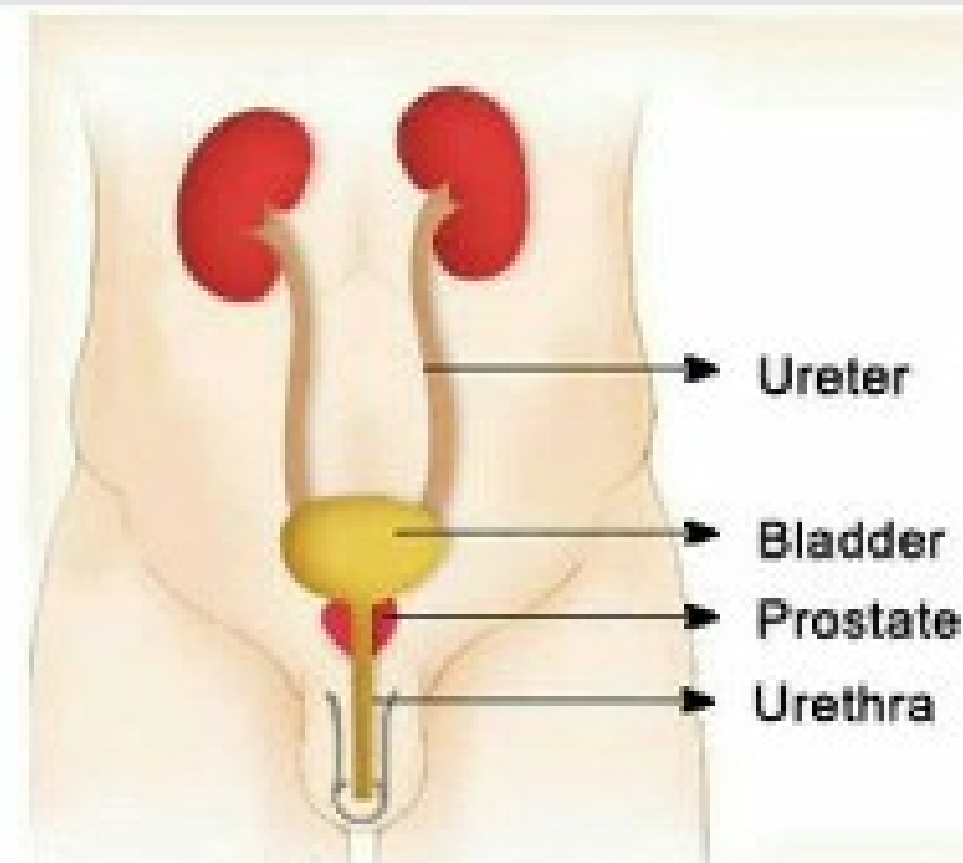
Thiazides are taken orally as part of the patient's regular medication. **Indapamide** (e.g. 2.5 mg daily) and **Chlortalidone** (12.5–25 mg daily) are recommended for hypertension.

Higher dose treatment tends just to increase side effects without significantly improving the antihypertensive effect.



Administration

It is generally best to take the tablet in the **morning**, so that the diuretic effect is maximal during the day rather than at night and does not therefore interfere with sleep.

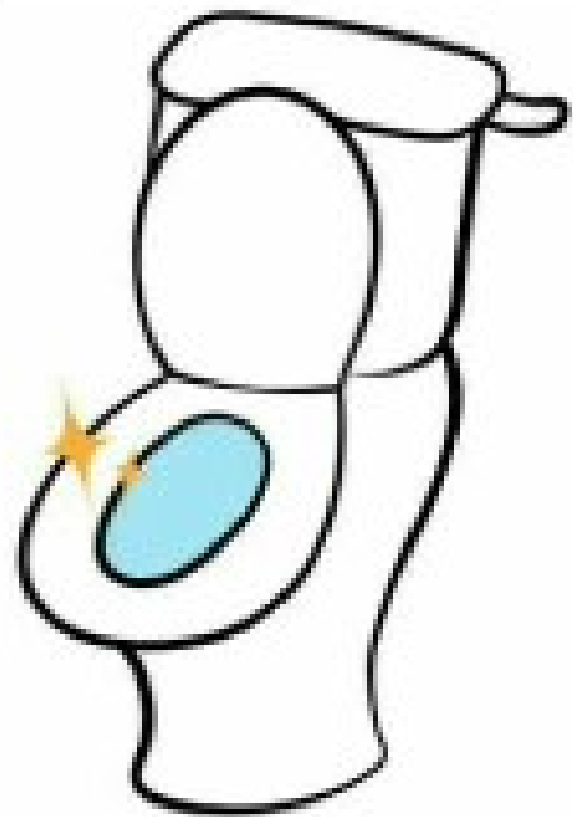


Patient education



Explain to your patient that you are offering treatment with a diuretic for their **high blood pressure**. If they have leg swelling, it may also help with this.

Patient education



Enquire whether they have any **difficulty getting to the toilet in time** (either because of mobility issues or sensations of urgency), since the diuretic is likely to make them pass water more often.

Patient education



Advise patients that **Anti-inflammatory Drugs** like **ibuprofen**, which can be bought without prescription, may interact with the diuretic and interfere with the way it works.

Patient education



Ask men directly about the possible side effect of **impotence**, as this may not be volunteered without prompting.

Monitoring of the treatment

- ① The best measure of efficacy is the patient's **blood pressure** and, if applicable, the severity of their oedema.
- ② **Measure the patient's serum electrolyte concentrations** before starting the drug, at 2–4 weeks into therapy, and after any change in therapy that might alter electrolyte balance.



Clinical tip

The combination of a thiazide and an ACE inhibitor/ARB can be very useful in practice.

One of the main adverse effects of **Thiazides** is hypokalemia, while one of the main adverse effects of **ACE inhibitors** and ARBs is hyperkalaemia.

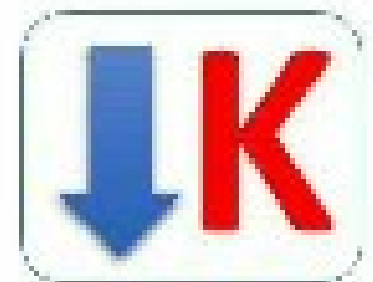
These drug classes have a synergistic blood pressure lowering effect: thiazides tend to activate the renin-angiotensin system, while ACE inhibitors/ARBs block it.



Licorice has compounds with aldosterone-Like activity thus it tends to cause potassium loss, and when used in combination with **a thiazide diuretic** (that also causes hypokalemia), licorice can increase their hypokalemic effect. The resultant hypokalemia may aggravate the tendency toward cardiac arrhythmia, **especially in people taking digoxin** (Lanoxin).



Licorice tend to aggravate the hypokalemic effect of thiazide diuretics.



Trimethoprim, an inhibitor of renal cationic secretion, can decrease the renal tubular secretions of thiazide diuretics to raise their blood levels and adverse effects.

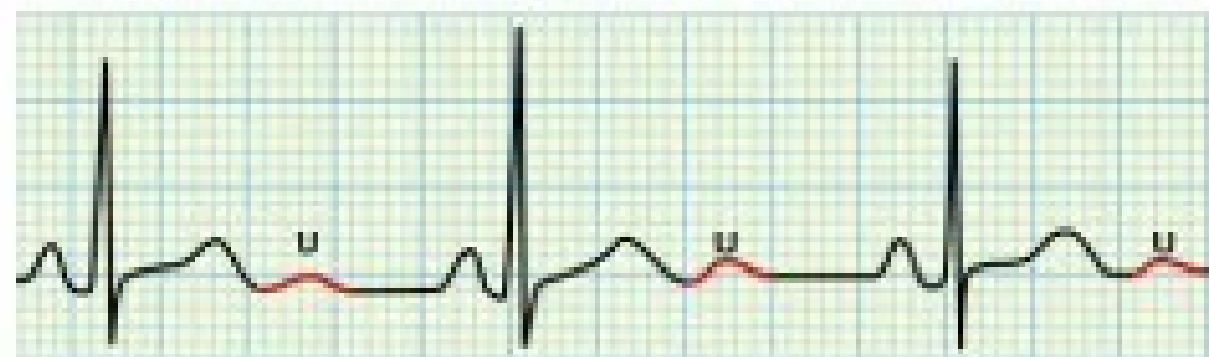
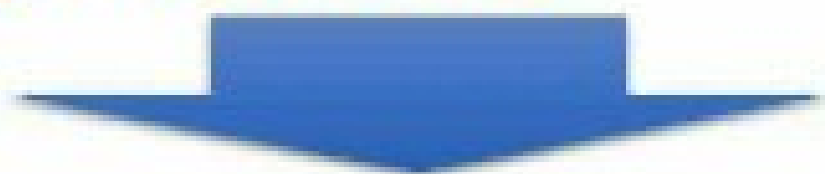


Note:
Trimethoprim may increase the adverse effects of thiazide diuretics.

Digoxin: Both hydrochlorothiazide and trichlormethiazide increase renal excretions of potassium to cause hypokalemia, a condition that increases the arrhythmogenic tendency of digoxin.



Corticosteroids tend to cause depletion of potassium. Therefore, co-administration with a potassium-depleting **thiazide diuretic**, such as hydrochlorothiazide, can lead to excessive **hypokalemia**.



Hypokalemia may cause muscular weakness, muscle cramps, myalgia, and even flaccid paralysis of muscles.

